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Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.01/D1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH K22NS104234
Blackman Family Fund for MS
Robert J. and Nancy D. Carney Endowment
Carney Graduate Award in Brain Science

Title: Investigating extrinsic regulators of oligodendrocyte generation during development

Authors: *G. M. MOLICA[1], S. R. MAYORAL[2];
[2]Neurosci., [1]Brown Univ., Providence, RI

Abstract: Myelin is an insulating sheath that wraps axons allowing for quick, efficient neuronal communication. In the central nervous system (CNS), myelin is made by specialized glia known as oligodendrocytes (OLs). The capacity of OLs to myelinate depends on the differentiation of oligodendrocyte precursor cells (OPCs) into mature OLs. During development, OL generation appears to proceed in a tightly regulated, spatiotemporal manner across the CNS. It begins to occur first in developing white matter tracts, such as the optic nerve (ON). Studies have shown that OL generation will occur in the absence of neuronal activity, strongly suggesting that non-neuronal signals determine the timing of OL generation. To investigate these signals and their source in an unbiased manner, we sequenced mRNA transcripts from the nuclei of mouse ONs on postnatal day 2 (P2) - prior to OL generation onset - and P7 - following OL generation onset. Single nucleus RNA sequencing revealed a detailed oligodendroglial (OLG) developmental trajectory via expression of canonical OLG markers, which validates the dataset's biological relevance. The OLG lineage was then used to build a pseudotime trajectory, from which co-expressing gene modules were identified. Gene ontology (GO) analysis of these modules shows terms related to myelination initiation, such as cholesterol metabolism, actin filament regulation, and signal transduction pathways. To begin uncovering processes that potentially regulate OL generation, we looked to other cell types. Astrocytes exhibited the most transcriptional changes besides OLG, positioning them as the most likely candidates for influencing OL differentiation. Cell-cell interaction analysis between OLG and astrocytes shows many strong, inferred interactions among the cells across development. Further effort to understand signaling roles through "sender" and "receiver" analysis reveals 35 significant pathways. Of these, the top pathways in which astrocytes are senders and OLG are receivers were picked as candidates potentially regulating OL generation. The necessity and sufficiency of these pathways in OL generation will be further tested using in vitro astrocyte-OPC co-culture systems. Altogether, single nucleus RNA-sequencing reveals that the early developing ON is a complex and rapidly changing environment. We use the dataset to first understand OLG lineage development in the early life ON, and then to begin elucidating signals that potentially drive OL generation. Inferred

astrocyte-OLG interactions show many avenues for investigation, with the most novel being a WNT ligand not yet described in this context.

Disclosures: G.M. Molica: None. **S.R. Mayoral:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.02/D2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01GM127431
NIH Grant R01MH130544

Title: Histone Demethylase KDM6B Promotes Postnatal Oligodendrocyte Maturation and Cortical Myelination

Authors: *J. HE[1], Z. SHEN[2];
[1]Michigan State Univ., East Lansing, MI; [2]Michigan State Univ., East Lansing, MI.

Abstract: Postnatal cortical myelination depends on epigenetic mechanisms that activate oligodendrocyte gene networks. Here we show that the histone H3K27me3 demethylase KDM6B is required for this process *in vivo*. Conditional deletion of ***Kdm6b*** in Emx1^{+} dorsal telencephalic progenitors delayed cortical myelination and impaired postnatal oligodendrocyte maturation. Although oligodendrocyte precursor cell density was unchanged, pre-myelinating and mature oligodendrocyte markers were markedly reduced. Lineage-specific RNA-seq revealed early suppression of ***Sox10***, a master regulator of oligodendrocyte maturation, followed by downregulation of myelin-associated genes. Consistent with this, chromatin immunoprecipitation showed increased H3K27me3 at promoter-proximal regions of ***Sox10*** in the same lineage. Temporally controlled ***Sox10*** induction partially rescued myelination in ***Kdm6b***-deficient mice. These findings identify a KDM6B→SOX10 axis that promotes postnatal oligodendrocyte maturation and cortical myelination by limiting repressive H3K27me3 at a key upstream regulator, with implications for KDM6B-related neurodevelopmental disorders.

Disclosures: J. He: None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.03/D3

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIRM [EDUC4-12802]
NINDS R01NS126981

Title: Prenatal inflammation alters fetal oligodendrocyte precursor cell developmental waves through microglial signaling

Authors: *H. HORACKOVA, J. CROSTHWAIT, Y. LIU, J. ALVAREZ, A. BONNIN; Children Hosp. Los Angeles, Saban Res. Institute, Univ. of Southern California, Los Angeles, CA

Abstract: Axonal myelination is critical for neurologic function and relies on a self-renewing pool of oligodendrocyte precursor cells (OPCs). OPCs arise from three consecutive developmental waves and differentiate into myelinating oligodendrocytes. Rodent studies show that maternal inflammation disrupts oligodendrocyte lineage progression and myelination, while human epidemiologic studies further link fetal exposure to maternal inflammation to increased risk of neurologic sequelae such as cerebral palsy. However, whether and how maternal inflammation selectively alters specific developmental OPC waves remains unclear. We injected pregnant mice with poly(I:C) at gestational day (GD)13 to mimic a viral infection. At GD15, we observed reduced 1st wave OPC density in the medial ganglionic eminence (MGE), and entopeduncular nucleus (EPN), accompanied by increased morphological complexity, a feature normally associated with more highly differentiated OPC states. By GD17, we observed increased density and reduced Ki67^{+} proliferation of 2nd wave OPCs in the cortex, suggesting over-compensation. By postnatal day (PD)30, total brain OPC density was decreased, whereas mature myelinating oligodendrocytes were increased. Consistent with a lineage shift induced by inflammation, we observed hypermyelination in motor cortex using MBP immunostaining and electron microscopy. Importantly, pharmacological COX-2 inhibition and microglia-specific *Ptgs2* deletion rescued the fetal OPC phenotype at GD15. Together, these findings suggest that prenatal inflammation differentially affects developmental OPC waves and shifts oligodendrocyte lineage progression toward accelerated maturation and increased myelination. Mechanistically, microglial prostaglandin signaling contributes to inflammation effects on fetal OPC phenotype. By linking *in utero* alterations in oligodendrogenesis to long-term changes in myelination, this work reveals a potential developmental origin of altered oligodendrocyte lineage and myelin outcomes.

Disclosures: H. Horackova: None. **J. Crosthwait:** None. **Y. Liu:** None. **J. Alvarez:** None. **A. Bonnin:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.04/D4

Topic: A.01. Neurogenesis and Gliogenesis

Support: 5R01MH052716-30
5R01DA039062-10

Title: Sex chromosomes, there's more than meets the SRY: How sex chromosome complement influences sex differences in microglia in the developing rat amygdala

Authors: *G. VOITHOFER[1], M. M. MCCARTHY[2], D. A. BANGASSER[3], A. P. ARNOLD[4], E. P. HARRIS[3], X. CHEN[4];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Dept. of Pharmacol., Univ. of Maryland Schoold of Med., Baltimore, MD; [3]Ctr. for Behavioral Neurosci., Georgia State Univ., Atlanta, GA; [4]Dept. of Integrative Biol. & Physiol., Univ. of California, Los Angeles, CA

Abstract: Sex differences established in neurodevelopment are often attributed to neonatal androgen exposure derived from the fetal testis, whose development is directed by the presence of the sex-determining region Y (SRY) gene. However, VanRyzin et al. (2024) [BioRxiv; DOI: 10.1101/2024.08.19.608675] have discovered a novel mechanism in which microglia-derived TNF- α actively femininizes astrocytic density in the medial amygdala (MeA) during the first week of postnatal life. Females are not exposed to systemic sex steroids during this period of development, warranting additional investigation into sex chromosomes and how they may influence the establishment of sex differences in microglia activity. During the first week of postnatal life, there is increased density of phagocytic microglia in the MeA of males compared to females. We sought to determine whether the sex chromosome complement contributes to this sex difference in microglial phagocytic density. Using a four-core genotype (FCG) rat model in which the SRY gene has been inserted into an autosome, we conducted immunofluorescent imaging of microglia in MeA. We determined that phagocytic capacity in the MeA of XX SRY+ males was intermediate between XY WT males and XX WT females. Semiautomated analysis of microglia morphology utilizing Kim et al. (2024) [eNeuro; DOI: 10.1523/ENEURO.0014-24.2024] ImageJ and RStudio high-throughput pipeline indicated a trending difference in the composition of microglia subtypes for the FCG rats. XY WT male microglia, on average, had a more ramified/transitional phenotype, while microglia in XX WT females were more ameboid, and XX SRY+ males again had an intermediate morphology between the two WT genotypes. These findings are consistent with a novel role for sex chromosome complement in feminizing microglial morphology and phagocytic capacity in the MeA during neurodevelopment, in a brain region essential for social behavior.

Disclosures: G. Voithofer: None. **M.M. McCarthy:** None. **D.A. Bangasser:** None. **A.P. Arnold:** None. **E.P. Harris:** None. **X. Chen:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.05/D5

Topic: A.01. Neurogenesis and Gliogenesis

Support: JST SPRING, Grant Number JPMJSP2124

Title: The CNS-associated macrophages regulated by cGAS maintain meningeal architecture.

Authors: *C. HIRAKI[1], F. TSURUTA[2];
[1]Grad. Sch. of Life and Envrn. Sci., [2]Fac. of Life and Envrn. Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: CNS-associated macrophages (CAMs) are resident macrophages located in the meningeal subarachnoid space. Although CAMs populate the meninges from early embryonic stages, their functions during development remain poorly understood.Previously, we found that neuron-derived micronuclei are incorporated by brain macrophages during development, resulting in alterations of their cellular states. In microglia, these changes are rescued by deficiency of cyclic GMP-AMP synthase (cGAS), a cytosolic DNA sensor activated by micronuclear DNA. We also found that micronuclei are incorporated by CAMs. However, it remains unclear whether cGAS similarly regulates CAMs phenotypes during development. In this study, we investigated the role of cGAS in regulating developmental CAMs phenotypes using wild-type (WT) and cGAS knockout (KO) mice at postnatal day (P) 7-14. Immunostaining of P14 brain sections with CD206, a representative CAMs marker, showed reductions in both CD206 immunoreactivity and CAMs number in cGAS KO mice. To further characterize CAMs phenotypes, brain macrophages were isolated from WT and cGAS KO mice and analyzed by quantitative PCR. Expression of CAMs-associated genes, including Cd206 and Dab2, was reduced in cGAS KO mice, whereas expression of Lyve1 was unchanged. In addition, expression of extracellular matrix (ECM)-related genes was decreased in cGAS-deficient macrophages. Given that the meninges are enriched in ECM-producing fibroblasts and fibrous ECM structures, we examined the impact of cGAS deficiency on meningeal architecture. Meningeal sections were stained with phosphotungstic acid hematoxylin (PTAH) to visualize fibrous structures. Quantitative analyses showed a significant reduction in fibrous structures within the subarachnoid space of cGAS KO mice compared with WT. These findings suggest that cGAS contributes to the regulation of developmental CAMs phenotypes and is associated with the formation of fibrous meningeal structures. Our results provide evidence that developmental CAMs influence the meningeal environment and identify a potential role for the micronucleus-cGAS pathway in meningeal development.

Disclosures: C. Hiraki: None. **F. Tsuruta:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.06/D6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R01NS130035-04

Title: Schwann cell LGI4 signaling regulates translational control of metabolic and post-transcriptional programs during sensory neuron maturation

Authors: *H. ARAIN[1,2], Y. ZHANG[3], J. L. SALZER[4];
[1]New York Univ. Grossman Sch. of Med., New York, NY; [2]Neurosci., Columbia Univ. Vagelos Col. of Physicians and Surgeons, New York, NY; [3]Neurosci. Inst., [4]Dept Neurosci. and Physiol., NYU Langone Med. Ctr., New York, NY

Abstract: Glia perform a wide range of functions that promote neuronal survival and function, including shaping early neuronal differentiation and development. Although Schwann cells are well known for their critical role in peripheral nervous system myelination, their broader roles-and the molecular mechanisms by which they influence neuronal growth and maturation-remain incompletely understood. Here, we study the glial claw paw mutant, in which dysfunction of the Schwann cell signaling protein LGI4 leads to dorsal root ganglion (DRG) sensory neuron cell death, along with delayed gliogenesis, glial differentiation, and peripheral nervous system myelination. To elucidate the molecular mechanisms underlying these effects, we used TRAP-seq to characterize translatomic changes in parvalbumin-positive DRG neurons from mutant mice relative to controls. After identifying significantly altered expression of interrelated metabolic and regulatory targets at P10, we used immunohistochemistry (n = 10) to confirm marked changes in key post-transcriptional regulators, including DDX5 and PTBP1, as well as effectors of the mTOR signaling pathway, including phospho-p70 S6 kinase and phospho-4E-BP1. We further used iDISCO embryonic tissue clearing across three developmental time points to identify the onset of DRG sensory neuron cell death at E13.5 (n = 6). Together, these findings suggest that Schwann cell LGI4 signaling is required not only for myelination but also for maintaining the metabolic and post-transcriptional regulatory state of developing sensory neurons, implicating glial-derived signals as broad determinants of peripheral neuron phenotype.

Disclosures: H. Arain: None. **Y. Zhang:** None. **J.L. Salzer:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.07/D7

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01HD092593

Title: Altered maternal-fetal cholesterol transport impairs offspring neurodevelopment

Authors: *W. YAKAH, C.-M. VACHER, A. A. PENN;
Pediatrics, Columbia Univ., New York, NY

Abstract: Cholesterol is essential for fetal brain development, supporting membrane biogenesis, steroidogenesis, and myelination. During pregnancy, the fetus relies in part on maternally supplied cholesterol for growth; however, whether maternal cholesterol crosses the placenta, reaches the fetal brain, and shapes long-term offspring neurodevelopment remains poorly understood. In a prospective human cohort study, we observed that lower circulating cord blood cholesterol levels were significantly associated with worse neurobehavioral outcomes in 4-6-year-old children. To explore further, we created a trophoblast-specific Cyp19a1-driven Abca1/Abcg1 knockout (Abca1/g1^{Cyp19}KO) mouse model of decreased cholesterol efflux to investigate whether reduced maternal-fetal cholesterol transport alters fetal brain cholesterol availability and shapes later neurodevelopmental outcomes. Stable isotope tracing with maternally administered deuterated (d7)-cholesterol showed that maternally derived cholesterol is detectable in fetal tissues (via LC-MS), including the fetal brain, demonstrating direct transfer from the maternal circulation to the developing brain. Abca1/g1^{Cyp19}KO brains showed a 31% reduction in d7-cholesterol at E14 (following maternal injection at E12). Postnatally, Abca1/g1^{Cyp19}KO mice exhibited impaired peripheral and central cholesterol homeostasis in a sex-dependent manner, with male offspring showing persistent reductions in circulating cholesterol and altered sterol-pathway regulation. Consistent with these changes, male Abca1/g1^{Cyp19}KO mice exhibited reduced cholesterol and its biosynthetic intermediates in myelin at postnatal day (P) 21 and P42 relative to littermate controls, along with a reduced latency to fall on the rotarod test. Together, these findings indicate that disrupted placental cholesterol transport during gestation alters fetal brain cholesterol levels and produces lasting changes in brain cholesterol metabolism, myelination, and behavior in a sex-linked manner.

Disclosures: W. Yakah: None. **C. Vacher:** None. **A.A. Penn:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.08/D8

Topic: A.01. Neurogenesis and Gliogenesis

Support: 2R01MH052716-26 to MMM

Title: An intricate dance: necessity of microglia for mast cell retention in the developing rat brain.

Authors: *K. ENGEL[1], M. M. MCCARTHY[2];
[2]Dept. of Pharmacol., [1]Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: A transient and highly proliferative population of mast cells (MCs) reside within meningeal spaces such as the velum interpositum (VIP) during early postnatal development. Their numbers peak around postnatal day 7 (PN7) and steadily decline until they disappear by PN30. These innate immune cells are canonically known for mediating allergic responses

through the secretion of histamine stored in their granules. During MC residence in the VIP, we found that they undergo constitutive piecemeal degranulation, releasing various factors into the local environment that can impact neighboring cells. Microglia, the brain's resident immune cell, is a subtype of macrophage that's heavily implicated in physiological neurodevelopment. Previous work demonstrated that experimentally inducing MC degranulation on PN2 reduces microglial proliferation within the VIP (PMID: 39662467), suggesting a functional interaction between MCs and microglia. Compelling new data indicates depletion of microglia using clodronate liposomes (clodronate) on PN0 and PN1 results in a persistent reduction in MC numbers throughout the first two postnatal weeks compared with empty liposome-treated controls (vehicle). Importantly, clodronate does not directly affect MC survival or proliferation, as it neither induces MC apoptosis nor reduces their proliferative capacity. Microglial depletion also decreases mast cell progenitors (MCPs) and MC numbers in other meningeal compartments, including the pia and dura mater, while sparing MC populations within the hypothalamic brain parenchyma. These findings suggest that, in the absence of macrophages/microglia, MCs and MCPs fail to be retained within meningeal spaces. Further analysis suggests that they may be migrating to peripheral tissue, such as the deep cervical lymph node, leaving only one-third to one-half of the original MC population. Together, these observations support the **hypothesis that microglia play a critical role in promoting the residence and maintenance of MCs within meningeal spaces during early postnatal development.**

Disclosures: K. Engel: None. **M.M. McCarthy:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.09/D9

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01MH052716-30
R01MH052716-29S1

Title: Mast Cells in the Developing Hippocampus: Gatekeepers of Neurogenic Expansion

Authors: *A. ALLEE[1], M. M. MCCARTHY[2];
[2]Dept. of Pharmacol., [1]Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Early life inflammatory events are consistently linked to neurodevelopmental disorder diagnosis, and the implication is straightforward: immune activation during neurodevelopment has consequences. These consequences are varied and their causes are largely unknown, but consistently, microglial contributions are overrepresented in the literature, with other immune cell contributions poorly defined. Using the Sprague Dawley rat as a model, we characterized a population of mast cells proximal to the hippocampal neurogenic niche, termed peri-hippocampal mast cells (phMCs). phMC population expansion is rapid and robust, as these cells

proliferate and peak in number at postnatal day (PN) 7, steadily decline until PN14, and become undetectable by the third week of life: a pattern reminiscent of a critical developmental window. Temporally, the phMC population peak coincides with the peak of hippocampal neurogenesis. Thus, we hypothesize that phMCs promote hippocampal neurogenesis via two non-exclusive mechanisms: direct action of phMC-released mediators on neural progenitors, and indirect remodeling of the local microenvironment through histamine-dependent blood-brain barrier (BBB) permeability and regulation of microglial phagocytic behavior. Degranulation at PN2 caused region-specific, histamine-dependent leakage of peripherally injected 70-kDa tracers into the hippocampus, but not the cerebellum, whereas at PN7 tracer leakage was restricted to molecules ≤10-kDa. phMC degranulation on PN5-7 resulted in a significant increase in microglial phagocytic activity at PN9, suggestive of efferocytosis of apoptotic progenitors. Notably, this phagocytic activity was directed away from immature neurons. Consistent with redirected phagocytic activity, phMC degranulation resulted in a significant increase in BrdU+NeuN+ neurons in the dentate gyrus at PN14.
These findings demonstrate that phMCs actively shape hippocampal neurogenesis, microglial phagocytic behavior, and BBB permeability within a narrow, developmentally constrained window. phMCs have the functional capacity to dictate hippocampal BBB permissiveness to molecules of different sizes, with larger molecules gaining entry at PN2, before access becomes size-restricted by PN7, consistent with a maturing hippocampal BBB. Together, these findings position phMCs as a regional cellular governor of the hippocampal neurogenic niche.

Disclosures: A. Allee: None. **M.M. McCarthy:** None.

Poster

PSTR296: Glial Development

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.10/D10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R35GM142368
NIH Grant R01ES035013

Title: Leigh syndrome mouse model with impaired Complex I activity displays postnatal defects in neuro/oligogenesis and white matter development

Authors: *S. BISWAS[1], P. L. TOMSICK[1], C. KELLY[1], B. A. LESTER[1], J. P. MILNER[1], S. N. HENRY[2], S. BRINDLEY[1], P. D. MORTON[2], A. M. PICKRELL[1];
[1]Sch. of Neurosci., [2]Dept. of Biomed. Sci. and Pathobiology, Virginia Polytechnic Inst. and State Univ., Blacksburg, VA

Abstract: Leigh syndrome (LS) is the most common pediatric presentation of primary mitochondrial disorders involving the neuromuscular system. Researchers and clinicians primarily focus on the neurodegenerative lesions that characterize the disease, even though

developmental delays often precede the onset of neurodegenerative symptoms. We sought to determine whether sustained mitochondrial dysfunction affected key processes involved in early postnatal brain development, including neurogenesis, gliogenesis, and myelination. In the *NDUFS4* knockout (KO) mouse, a widely used model of LS with a Complex I deficiency, we observed delayed postnatal brain growth, characterized by a lag in achieving mature brain weight and size. Our investigation within the neurogenic subventricular zone (SVZ) revealed an early reduction in neural stem cells (NSC) and neuroblast populations at postnatal day (P14), followed by impaired lineage progression at later time points. This reduction was primarily driven by impaired stem cell proliferation as indicated by reduced density and proportion of proliferating NSCs and reduced proliferative capacity of KO NSCs *in vitro*. To investigate the cell type-specific effects of Complex I deficiency, we performed single-cell RNA sequencing (scRNA-seq) of the SVZ. Differential expression analyses of KO NSCs and transit-amplifying progenitors revealed widespread suppression of gene networks involved in neurogenesis, oligogenesis, and myelination. The overall abundance of oligodendrocyte progenitor cells (OPCs) and mature oligodendrocytes within the dorsal SVZ remained unchanged. However, neural progenitor populations originating from SVZ domains that serve as major sources of OPC production and contribute substantially to corpus callosum (CC) development were markedly reduced. In addition to decreased oligogenesis, we observed decreased expression of myelin basic protein (MBP) in both scRNA-seq data and myelin staining, accompanied by reduced CC thickness. Consistent with this, KO mice exhibited reduced compact myelin in the CC, as measured by spectral confocal reflectance (SCoRe) microscopy, throughout the developmental myelination period. These findings warrant further investigation to determine whether the observed deficit results from dysmyelination, demyelination, or a combination of both processes. Overall, our observations indicate defects in postnatal neural/glial progenitors and myelination, events that precede neurodegeneration, which may warrant a reevaluation of current views on LS pathogenesis.

Disclosures: S. Biswas: None. **P.L. Tomsick:** None. **C. Kelly:** None. **B.A. Lester:** None. **J.P. Milner:** None. **S.N. Henry:** None. **S. Brindley:** None. **P.D. Morton:** None. **A.M. Pickrell:** None.

Poster

PSTR296: Glial Development

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR296.11/D11

Topic: A.01. Neurogenesis and Gliogenesis

Title: Developmental Remodelling of the Dystrophin Glycoprotein Complex Reveals CNS Specific Architecture

Authors: *R. R. ALKHARJI[1], A. ALHAMDI[2];
[1]Res. department, Natural and Hlth. Sci. Res. Centre, Princess Nourah bint Abdulrahman Univ., Riyadh, Saudi Arabia; [2]pharmacology, Univ. Col. London, London, United Kingdom

Abstract: The dystrophin- glycoprotein complex (DGC) is traditionally viewed as a structural stabilizer in skeletal muscle, yet emerging evidence indicates it also functions as a developmentally dynamic signalling scaffold in the human brain. Its spaciotemporal regulation during neurodevelopment and how these processes intersect with CNS phenotypes in Duchenne muscular dystrophy (DMD) remains poorly defined. Here, we provide the first multi-omics, lifespan-resolved dissection of DGC architecture in the human brain. We analysed 21 DGC-associated genes, including **dystrophin (DMD), dystroglycan 1 (DAG1), sarcoglycans (SGCA-SGCZ), syntrophins (SNTA1, SNTB1, SNTB2, SNTG1, SNTG2), dystrobrevins (DTNA, DTNB), and associated partners such as nitric oxide synthase 1 (NOS1) and ankyrins (ANK2, ANK3).**Across prenatal (HDBR, 4-20 PCW) and adult (GTEx v8) transcriptomes, we identify coordinated developmental remodelling of DGC components. Ten core genes are foetal-enriched, with SNTG2 showing the strongest foetal dominance, while SGCA, SNTA1, DTNA, and DTNB undergo robust adult upregulation, including 343-fold cerebellar enrichment of SGCA. The foetal period is marked by **SNTB2 to SNTG1 syntrophin switching** and an **18-fold increase in the SNTA1/SNTB2 ratio**, indicating a transition from a foetal structural DGC to an adult synaptic signalling complex.Single-cell analysis reveals cell type specific segmentation of DGC function, with neuronal and oligodendrocyte enrichment of most components and astrocyte specific expression of DAG1 and SGCB. Integrating these findings with our DMD iPSC-derived neural models, we observe DAG1 downregulation and disturbance of α/β-dystroglycan protein in DMD NPCs, neurons, and astrocytes, consistent with destabilization of the glial DGC in the absence of dystrophin isoforms.Protein-interaction analysis identifies NOS1 as a central DGC-linked signalling hub, connecting dystrophin-syntrophin complexes to NMDA receptor regulation, calcium homeostasis, and long-term potentiation. Pathway enrichment implicates the DGC in circadian entrainment, synaptic plasticity, ECM-receptor signalling, and neurodevelopmental risk networks.Together, these findings establish the DGC as a developmentally regulated, isoform-switching CNS scaffold whose remodelling shapes synaptic signalling and glial-neuronal interactions, providing new insight into how DGC disruption may contribute to CNS phenotypes in DMD.

Disclosures: R.R. Alkharji: A. Employment/Salary (full or part-time):; Research department, Natural and Health Science Research Centre, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.. **A. Alhamdi:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.01/D12

Topic: A.06. Developmental Disorders

Support: NIH Grant R15S088776

Title: Early-Life Stress and Neonatal Status Epilepticus Differentially Alter Communication Behaviors in Male and Female Mice

Authors: *S. PELL[1], T. BRADISH[1], C. LAU[1], B. CHESLEY[1], T. GARCIA[1], A. GARAPATI[1], A. ADARI[1], J. J. THAYIL[1], T. SANDERS[1], K. BLANDIN[2], J. N. LUGO, Jr.[3];
[2]Psychology & neuroscience, [3]Psychology and Neurosci., [1]Baylor Univ., Waco, TX

Abstract: Status epilepticus (SE), whose incidence is highest before the age of two, is defined as a seizure lasting longer than five minutes or a cycling of seizures without the recovery of consciousness between them. A single episode of SE can increase the risk of neuronal degeneration and can lead to long-term neurological deficits. In addition, early-life stress from impoverished environments is a significant contributor to adverse neurodevelopmental outcomes and increases the risk of neurodevelopmental delays. Seizures and stress in early-life have been individually linked to communication deficits. We wanted to investigate whether seizures and stress would have an additive effect, as well as investigate sex differences in response to developmental insults. We used male and female C57BL/6J mice to investigate the role of a single neonatal episode of status epilepticus and stress on communication behavior. On postnatal days (PD) 2-9, mouse pups and the dam were either exposed to the limited bedding and nesting paradigm or left in a control housing environment. On PD10, mouse pups were separated from the dam and either given an injection of 0.5% kainic acid, to induce SE, or saline. Ultrasonic vocalizations (USVs) were run on PD 12 to assess differences in call types and the spectral properties of calls. Analysis of the distribution of call types showed interactions between kainic acid and stress, such that SE following stress increased the number of flat, frequency step, and short calls compared to saline. Kainic acid without stress showed an increase in chevron, complex, and upward calls compared to the saline, no stress group. Stress with or without SE showed increases in composite and unstructured calls compared to the no stress group. We found significant sex effects where female mice with SE showed an increase in frequency steps, two-component, and unstructured calls compared to males. Stressed females had increased composite and frequency step calls, whereas stressed males had increased short and unstructured calls compared to each other. Stress increased downward calls for both sexes. We did not find any significant differences in spectral properties (total calls, mean call duration, total duration, latency to first call, principal frequency, and mean power) of USV calls. Our results suggest that neonatal stress and SE can have lasting additive effects on communication behavior. The findings also highlight sex differences in response to early-developmental insults. The results offer deeper insights into developmental trajectories following neonatal SE and stress.

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Poster

PSTR297: Animal Models of Autism

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Program #/Poster #: PSTR297.02/D13

Topic: A.06. Developmental Disorders

Support: NIH Grant R15S088776

Title: Neuron subset-specific-Pten deletion disrupts normative and reward-related behaviors in a mouse model

Authors: *C. LAU[1], S. PELL[1], T. GARCIA[1], K. LALLY[1], L. COAST[1], M. HEMMERSMEIER[1], A. GARAPATI[1], J. J. THAYIL[1], C. ENYERIBE[1], T. BRADISH[1], K. BLANDIN[2], J. N. LUGO, Jr.[3];
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Abstract: Depression commonly co-occurs with epilepsy and autism spectrum disorder (ASD). Dysregulation of the mechanistic target of rapamycin (mTOR) signaling pathway has been implicated in both neurodevelopmental disorders. Deletion or mutation of phosphate and tensin homolog (*PTEN*), a negative regulator of mTOR signaling pathway, has been associated with epilepsy, ASD phenotypes, and altered neurodevelopment. In the present study, we used four commonly run depressive-like rodent tasks in male and female neuron subset-specific-*Pten* knockout (KO) mice and wildtype (WT) mice. These tasks include splash test (n=14), novelty suppressed feeding (n=14), nest-building test (n=14), and sucrose preference test (n=11). During splash test, mice were sprayed with 2% sucrose solution and grooming behavior was recorded for 5 minutes and analyzed using BORIS software. A two-way ANOVA revealed a significant sex and genotype interaction for body grooming duration. Female KO mice exhibited increased body grooming duration relative to WT females, while male KO mice exhibited reduced grooming duration relative to WT males. No significant effects were observed for body grooming duration or head and body grooming frequency. For the novelty suppressed feeding task, latency to feed in a novel cage and home cage was measured after mice were food deprived for 24 hours. KO mice took significantly longer to start eating in the home cage than WT, whereas latency to feed in the novel environment did not significantly differ between groups. In the nest-building task, mice were individually housed for 18 hours overnight and given a 3.0g nestlet. Nest quality was scored on a 5-point scale, and untorn nestlet percentage was calculated. KO mice had significantly impaired nesting behavior characterized by reduced nest scores and increased untorn nestlet percentages compared to WT mice. In the sucrose preference test, mice were water-deprived for 24 hours prior to the experiment. On the test day, mice were given access to both a 2% sucrose solution and water. KO mice had significantly reduced sucrose water consumption relative to WT mice, while regular water consumption did not differ across groups. Together, these findings demonstrate that the neuron subset-specific-*Pten* deletion produces robust impairments in self-maintenance and reward-related behaviors, with select sex-dependent alterations in grooming behavior. Although these findings suggest altered affective and motivational processes, the severe phenotype and reduced lifespan observed in KO mice may also contribute to diminished behavioral performance independent of depressive-like behavior.

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Poster

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Title: Resting-state functional ultrasound reveals spatially localized prefrontal network alterations in a maternal immune activation mouse model

Authors: *K. HIKISHIMA[1,2], H. MIZUMA[3,4,5], T. TSURUGIZAWA[1], K. KASAHARA[1], T. GOTO[1], R. HAYASHI[1], H. ONOE[6,7], N. MIYASAKA[8], K. YOSHINAKA[1], N. NITTA[1];
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Abstract: Functional ultrasound imaging (fUSI) enables measurement of brain-wide hemodynamic fluctuations with high spatiotemporal resolution and has recently been used to map resting-state networks (RSNs) in awake rodents. However, its ability to detect disease-related alterations in functional brain networks remains unclear. Here, we investigated whether resting-state fUSI can identify spatially localized alterations in functional networks in a mouse model of neurodevelopmental disorders.. Maternal immune activation (MIA) mice exhibiting social interaction deficits and control mice were imaged under awake conditions. Relative cerebral blood volume (rCBV) images were acquired at 10 Hz in awake mice during the resting state using fUSI and processed using spatial masking to exclude non-neural regions (k-means clustering), spatial normalization to a stereotactic brain template, bandpass filtering (0.01-0.1 Hz), and independent component analysis to extract RSNs. Multiple RSNs were identified, including medial prefrontal, sensorimotor, and hippocampal networks. Among these, the medial prefrontal cortex (mPFC) network exhibited a significant increase in spatial extent in MIA mice compared with controls. Notably, voxel-wise analysis revealed that enhanced functional coupling was not uniformly distributed within the network but was spatially localized to the prelimbic cortex and adjacent cingulate and infralimbic regions. These localized alterations suggest that MIA-related effects on functional networks may manifest as subregional differences in coupling within the prefrontal cortex, rather than as uniform changes across networks. Furthermore, increased mPFC coupling showed a trend toward association with impaired social interaction behavior. Our findings demonstrate that resting-state fUSI enables the detection of region-specific functional connectivity abnormalities in awake mouse models of neurodevelopmental disorders. This approach may provide a useful framework for mapping region-specific network dysfunction associated with neurodevelopmental phenotypes.

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Poster

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Title: Maternal immune activation elicits regional choroid plexus responsein the developing brain

Authors: *T. E. LACEY[1], L. BYER[5], A. KWONG[2], J. BENSON[6], C. LAGARES LINARES[1], A. HOCHSTETLER[1], D. FIGUEROA VELEZ[1], H. XU[1], C. HEHNLY[3], M. GABRIELLE[1], M. ZAWADZKI[4], Y. COURTNEY[7], P. ARROYO MORALES[1], A. PRAGANA[8], M. LEHTINEN[1]; [1]Pathology, [2]Div. of Gastroenterology, Hepatology and Nutr., Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [3]Pathology, Boston Children's Hospital, Harvard Med. Sch., boston, MA; [4]Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [5]Pathology, Taipei Med. Univ., New Taipei, Taiwan; [6]Howard Univ. Med. Sch., Washington D.C., DC; [7]Stanford Univ., Campbell, CA; [8]Duke Univ. Neurobio. Grad. Program, Durham, NC

Abstract: Brain barriers are critical neuroimmune interfaces that protect the brain from peripheral blood-borne challenges, such as inflammation. However, brain-body communication during development is understudied. The choroid plexus (ChP), a blood-cerebrospinal fluid

(CSF) barrier present in each brain ventricle, is the primary producer of CSF, which is rich in spatiotemporally dynamic signaling molecules and cues critical for healthy brain development. Each of the ChP, lateral (LV), third (3V), and fourth (4V) ventricles, is morphologically distinct, transcriptionally heterogeneous, and comprises a diverse niche of cell types, including secretory epithelial cells and resident immune cells. Indeed, the LV and 4V ChP secrete distinct proteins into the CSF to specifically support the developmental needs of nearby CSF-contacting periventricular cells. Maternal immune activation (MIA) is an example of inflammation during brain development that increases the risk of several neurodevelopmental and neuropsychiatric disorders in offspring. Mouse MIA models exhibit embryonic parenchymal deficits and inflammation of the ChP-CSF axis. Still, which ChP is the most vulnerable barrier site, and its effects on ventricle-specific ChP secretion remain unclear. To address this gap, we investigated the early acute-to-post-acute ChP-CSF immune responses to viral-mimetic polyinosinic: polycytidylic acid (poly(I:C))- induced MIA. We characterized baseline regional differences in LV and 4V ChP immunological milieu across age. Using previously described metrics of ChP-CSF MIA-induced inflammation, we tracked early acute and post-acute maternal and embryonic CSF inflammation and measured relative LV and 4V ChP secretion *ex vivo* using multiplex cytokine ELISAs. We showed regionally distinct ChP immune cell population fluxes via spectral flow cytometry and tight junction responses to MIA using histological analyses across acute and post-acute timepoints, suggesting differential inflammation vulnerability. Overall, we have demonstrated spatiotemporally distinct responses and vulnerabilities of the LV and 4V blood-cerebrospinal fluid barriers following MIA. Future studies will determine whether targeting ChP ventricle-specific signaling during the maternal-fetal inflammation propagation time window will lessen the severity of MIA neuropathology.

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Poster

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Topic: A.06. Developmental Disorders

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Title: Gene x Environment interaction of Shank3 mutation and Polychlorinated Biphenyl exposure results in mixed behavioral phenotype and decreased dendritic complexity in a mouse model of Autism Spectrum Disorder

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Abstract: Prevalence of Autism Spectrum Disorder (ASD) rose from 1:68 children in 2010 to 1:36 children in the United States in 2020. Estimates indicate that increased awareness of ASD leading to more individuals being diagnosed accounts for 50% of the total rise in cases, leaving 50% attributable to other factors. Individuals with genetic risk factors for ASD exposed to environmental insults (gene x environment interactions) can unmask previously asymptotic ASD or increase severity in mildly symptomatic ASD. Here we utilize genetically vulnerable heterozygous Shank3 mutant mice exposed daily to a mixture of Polychlorinated Biphenyls (PCBS), a known neurotoxicant and candidate chemical for ASD risk. Wild type (WT) and heterozygous Shank3 (B6.129-Shank3tm2Gfng/J) mice of both sexes (n=10-15/group/sex) were orally dosed from weaning (p21) until six weeks of age (p42) with MARBLES PCB mixture at 0, 0.1, or 1mg/kg. ASD related behavioral phenotypes were assessed using social approach, repetitive grooming, and social odor discrimination. Brains were stained using FD Rapid GolgiStain kit, neurons from somatosensory cortex visualized, and Sholl analysis conducted. We recapitulate data demonstrating reduced sociability in Shank3 mutants to validate our ASD model in both male and female mice, with female mice exhibiting increased variability. PCB treatment in WT mice of both male and female sex had a mixed effect on behavioral phenotype assessment: social approach was unchanged, social odor discrimination showed a trend towards decreased time spent with social odors, and decreased repetitive grooming. Sholl analysis of cortical neurons showed decreased dendritic complexity and reduced AUC in male PCB treated mice and a trend towards decreased dendritic complexity in female mice. Preliminary results for PCB treated Shank3 mutant mice of both sexes show similarly mixed effects on behavioral phenotype assessment. Overall, PCB exposure did not increase ASD related behavioral phenotypes as hypothesized and, in some cases, reversed outcomes. Similarly, ex vivo and in vitro data predicted increased cortical complexity. However, in WT animals, cortical complexity decreased with PCB treatment. These results highlight the need for further investigation to determine the pathophysiological basis of gene x environment interactions in a juvenile model.

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Poster

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Title: Neural basis of pharmacological amelioration of social deficits in Fmr1KO mice during juvenile sensitive period

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Abstract: Background: Altered social functioning is a hallmark of Autism Spectrum Disorder (ASD), yet the developmental mechanisms remain poorly understood. Our recent work shows that adult male mice without Fmr1, the leading genetic cause of ASD, exhibit reduced sociability and blunted activities in medial prefrontal cortex (mPFC) neurons projecting to posterior paraventricular nucleus of thalamus (pPVT). Notably, the mPFC-pPVT circuit deficit, modulated by excessive inhibitory drive, emerges during the juvenile period and maintains into adulthood. Here we aim to investigate mechanisms underlying an early pharmacological intervention targeting juvenile mPFC-pPVT circuit to restore social function.
Method: We performed projection-specific transcriptomic profiling to identify molecular targets and define critical developmental windows for intervention. To investigate the mechanisms of candidate treatments, we combined immunohistochemistry, whole-cell patch-clamp electrophysiology, fiber photometry, and behavioral assays of social interaction.
Results: Projection-specific transcriptomics reveal GSK3β/β-catenin pathway dysregulation selectively in mPFC→PVT neurons. Notably, a single administration of lithium, a GSK3β inhibitor, during the juvenile period—but not adulthood—prevents long-term alteration in social behavior and enhances excitatory drive, restoring the excitatory-inhibitory balance. Our preliminary data further reveal lithium-induced molecular changes and real-time activity shifts of mPFC→pPVT neurons during social interaction.
Discussion: These findings define a sensitive window of circuit plasticity in Fmr1KO mice, and highlight the potential of early, circuit-targeted interventions to promote long-lasting adaptive social circuit function. Future work is warranted to elucidate the source of the increased excitatory drive following juvenile lithium administration which may uncover network-level plasticity mechanisms and guide the development of interventions that restore circuit function and promote social behavior.

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Poster

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Topic: A.06. Developmental Disorders

Title: Revisiting stimulus overselectivity in ASD: the BTBR mouse model shows reduced use of auditory cue during audio-visual compound processing

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Abstract: Stimulus overselectivity, a tendency to preferentially process only part of a complex stimulus comprising multiple elements, has been identified as a key characteristic of autism spectrum disorder (ASD) (e.g., Lovaas et al., 1971). Although a wide variety of ASD animal models have been developed, most studies have mainly focused on sociality and repetitive behaviour, highlighting the need to study higher-order cognitive characteristics of ASD in animal models. To broaden the currently limited scope of ASD animal-model research, we investigated whether overselectivity is shown in the BTBR mouse model of ASD. We used an operant conditioning procedure with an audio-visual compound discriminative stimulus (S^D) and assessed the relative control exerted by visual (light) and auditory (tone) elements. Experiment 1 examined S^D control of leverpressing by the audio-visual compound. 28 mice (14 male control mice and 14 male BTBR mice) were trained to leverpress during a compound S^D, followed by test sessions in which auditory and visual elements were presented separately. The visual and auditory elements exerted equally strong control over behaviour in the control C57BL/6J strain, whereas BTBR mice almost invariably (13/14 subjects) showed stronger responding to the visual element than to the auditory one. Experiment 2 examined whether the selective control by the visual cue in BTBR resulted from (1) training with an audio-visual compound (i.e., cue competition reflecting modality-specific overselectivity), or (2) intrinsically low salience or functionality of the auditory stimulus in BTBR, independent of compound training. To address this, we repeated the same experiment while including two additional groups trained with either light alone or tone alone. BTBR took significantly longer to acquire the discrimination with a tone-alone S^D, indicating that BTBR mice have a reduced ability to use tone as a S^D, regardless of whether the tone was trained within a compound. Furthermore, in BTBR, stimulus control by the tone was again weaker, being overshadowed by the light in the compound group. These findings indicate a weaker and more fragile control of instrumental behaviour by the auditory stimulus in BTBR, providing a new opportunity to investigate genetic and neural mechanisms underpinning sensory abnormalities widely observed in individuals with ASD, including hyper- and hyposensitivity to specific stimulus modalities. Also, the results may help develop more efficient interventions for individuals with ASD who present visually biased information processing.

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Poster

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Title: Paternal aging induces sex-dependent transcriptomic alterations in the embryonic mouse brain, with greater effects in females

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Abstract: Advanced paternal age is a recognized risk factor for autism spectrum disorder (ASD), yet the molecular mechanisms linking paternal aging to early neurodevelopment remain poorly understood. ASD in girls is often underrecognized, and female-specific mechanisms remain insufficiently studied. Whether paternal aging exerts sex-dependent effects on the embryonic brain also remains unclear. We performed bulk RNA sequencing based transcriptomic profiling of the embryonic day 14.5 mouse telencephalon in offspring derived from young (3-month) or aged (19-month) fathers, analyzing male and female offspring separately. Because developmental stage strongly influences embryonic brain gene expression, embryos were staged using the Embryonic Mouse Ontogenetic Staging System (eMOSS), based on hindlimb morphology. This revealed substantial variability in developmental progression even among embryos from the same litter, with an average difference of ~10 hours. From 106 embryos obtained from 13 independent litters, we selected six closely stage-matched embryos per group: young father-derived offspring (YFO) male, YFO female, aged father-derived offspring (AFO) male, and AFO female. Principal component analysis revealed that AFO female samples formed a distinct cluster separated from the other groups. Hierarchical clustering further indicated that both biological sex and paternal age contributed to transcriptomic variation, with paternal aging effects appearing more pronounced in females. Consistently, differential expression analysis showed only modest transcriptional changes in AFO males, whereas AFO females exhibited broader gene expression changes with an overall tendency toward upregulation. Consequently, male-female transcriptional divergence was more pronounced in the AFO condition than in the YFO condition. These findings indicate that paternal aging induces sex-dependent transcriptomic alterations during embryonic brain development and suggest that female offspring may show greater molecular susceptibility to paternal age-associated developmental perturbations. By focusing on female embryonic brain responses, this study may help address the underexplored biology of ASD in girls and contribute to a more sex-informed understanding of paternal age-associated ASD risk mechanisms.

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Poster

PSTR297: Animal Models of Autism

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Topic: A.06. Developmental Disorders

Support: MH138309

Title: Motor Behavioral Alterations as a Core Feature of Mouse Models of Neurodevelopmental Risk Genes

Authors: *T. P. NGUYEN[1], S. MURRAY[2], V. KUMAR[3];
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Abstract: Motor behavioral alterations, including gait abnormalities, postural instability, and deficits in coordination, affect 80-90% of individuals with autism spectrum disorder (ASD) and other neurodevelopmental disorders (NDDs), a prevalence comparable to the defining social communication deficits. Although these features are often described as associated motor dysfunction, NDD-related motor alterations may differ from classical overt motor impairments, instead manifesting as distinct patterns of movement, posture, and sensorimotor organization. Yet motor dysfunction remains classified primarily as an associated feature rather than a diagnostic criterion or specifier. Here, we review converging evidence from epidemiological studies, quantitative gait analysis, neuroimaging, and mouse genetics that challenges this classification. Mouse models carrying mutations in ASD/NDD risk genes, including Shank3, Cntnap2, Tsc1, Mecp2, Ube3a, Syngap1, Arid1b, Adnp, and Fmr1, exhibit gait, coordination, or postural phenotypes. Computer-vision-based deep phenotyping detects subtle motor signatures that traditional assays miss. We propose that the SSPsyGene consortium's systematic characterization of about 100 NDD risk genes using KOMP mouse lines, combined with high-throughput gait and posture analysis, will provide large-scale genetic evidence that motor behavior is a valid translational readout of NDD biology and strengthen the case for recognizing motor behavioral alteration as a diagnostic specifier in ASD.

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Poster

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Topic: A.06. Developmental Disorders

Support: 5R01MH110487-09

Title: Identification and rescue of myelination deficits in an ASD mouse model of Coffin-Siris Syndrome

Authors: *S. M. STUMP[1], J. F. BOHLEN[2], N. SADOWSKI[3], S. SHANKARAN[4], B. J. MAHER[5];

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Abstract: Autism spectrum disorder (ASD) is genetically heterogeneous with overlapping symptomatology, suggesting convergent dysregulated pathways. Core features of ASD include deficits in socialization, communication and behavior, and can present with other comorbidities such as intellectual disability (ID), epilepsy, anxiety, depression, attention deficits, and sleep disorders. Our lab has previously identified phenotypic differences in oligodendrocyte progenitor cells (OPCs) and oligodendrocytes (OLs) in a mouse model of Pitt-Hopkins Syndrome (PTHS), which is a rare form of ASD caused by mutations in the TCF4 gene. The goal of this study was to test the prevalence of myelination defects in ASD by determining if convergent phenotypes were present in mouse models of Coffin-Siris Syndrome (CSS), which is caused by mutations in the ASD risk gene *ARID1B* and is a genetic disorder characterized by developmental delay, impaired motor skills, low birth weight, ID, and delayed or absent speech and language. Primary OPC/OL cultures were derived from *Arid1b*$^{+/+}$ and *Arid1b*$^{+/-}$ littermates and we observed an increase in the proportion of OPCs (PDGFRα;+) and a decrease in OLs (CC-1+) in *Arid1b*$^{+/-}$ mice. A similar result was observed *in vivo*, as p24 and p42 mice showed a significant increase in OPCs and a significant decrease in mature OLs. Electron microscopy (EM) of the corpus callosum (CC) of P42 mice showed *Arid1b*$^{+/-}$ mice have a reduction in the density of myelinated axons. Compound action potential recordings from acute brain slices from *Arid1b*$^{+/-}$ mice showed that more action potentials were traveling down unmyelinated axons compared to *Arid1b*$^{+/+}$ littermates. Lastly, we performed rescue experiments by treating primary cultures or via i.p. administration of two different promyelinating compounds (clemastine, sobetirome/SOB-AM2). Treatment with clemastine or sobetirome/SOB-AM2 effectively rescued the proportions of OPC/OLs both *in vitro* and *in vivo*, the proportion of myelinated axons in the CC as measured by EM, and electrophysiology of the CC. Together, these results suggest that defects in the OL lineage and myelination may be a convergent pathophysiological mechanism in ASD that is amenable to therapeutic targeting.

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Poster

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Title: Generating knock-in mouse models to study pathogenic MAPK8IP3 variants and test disease reversibility

Authors: *Y. NONG[1], M. JOHNSON[2], B. MANGANO[1], R. VANDERPOOL[1], M. NADLER[3], H. NGUYEN[1], M. ZAYOUR[1], M. P. ANDERSON[4];
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Abstract: MAPK8IP3 encodes JNK-interacting protein 3 (JIP3), a protein for the c-Jun N-terminal kinase (JNK) signaling pathway and an adaptor that links organelles and vesicular cargoes to kinesin and dynein motor proteins. Through these functions, JIP3 regulates bidirectional microtubule-based axonal transport and intracellular signaling. More than 30 de novo pathogenic MAPK8IP3 variants have been identified and associated with neurodevelopmental disorders characterized by global developmental delay, cognitive impairment, motor dysfunction, and abnormal muscle tone. Structural brain abnormalities, including cerebral and cerebellar white matter deficits and corpus callosum hypoplasia, are also observed. However, the JIP3 domains responsible for these clinical manifestations remain unknown. Likewise, neural circuits underlying disease pathology and the potential for post-developmental therapeutic rescue have not been established. To address these questions, we generated multiple CRISPR-engineered knock-in mouse lines harboring disease-associated MAPK8IP3 variants, including an early truncating mutation (p.E27X) and two missense mutations (p.R579C and p.R1147C). Importantly, we developed a conditional, reversible p.R579C allele to investigate the reversibility of this autosomal dominant disorder. This strategy enables spatiotemporal and cell type-specific excision of the mutant allele while preserving wild-type expression using inducible Cre-ERT2 and cell type-specific Cre driver lines during both development and adulthood. Behavioral analyses of these heterozygous mutant mice showed divergent phenotypes. Male p.R579C and p.E27X mice exhibited reduced locomotor activity, including decreased travel distance and speed in open field test, whereas p.R1147C mice displayed robust hindlimb clasping. In contrast, none of the mutant lines showed alterations in time spent in the open arms of the elevated plus maze or latency to fall in Rotarod tests. These findings demonstrate that pathogenic MAPK8IP3 variants produce distinct neurological phenotypes, supporting unique functional roles for individual JIP3 domains. These novel mouse models provide a powerful platform for defining the mechanisms underlying JIP3-associated neurodevelopmental disorders. Moreover, this reversible p.R579C line offers a unique opportunity to determine whether correction of MAPK8IP3-dependent dysfunction within specific time windows and neural circuits can reverse established neurological deficits. These studies will inform ongoing therapeutic development efforts, including antisense oligonucleotide and genome-editing approaches.

Disclosures: Y. Nong: None. **M. Johnson:** None. **B. Mangano:** None. **R. Vanderpool:** None. **M. Nadler:** None. **H. Nguyen:** None. **M. Zayour:** None. **M.P. Anderson:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.12/E1

Topic: A.06. Developmental Disorders

Support: NIH RM1MH138309

Title: Mesoscale mapping unveils converging and diverging cellular architecture changes in mouse brains with neurodevelopmental disorder risk genes

Authors: *I. E. BJERKE[1], E. HAN[1], N. BLAHA[1], J. PI[1], T. LEACH[2], V. KUMAR[2], Y. KIM[1]; [1]Dept. of Neurosci. and Exptl. Therapeut., Penn State Univ., Hershey, PA; [2]The Jackson Lab., Bar Harbor, ME

Abstract: Recent genetic screening has identified more than hundreds of high confidence gene mutations linked to neurodevelopmental disorders (NDDs). Yet, it remains unclear how these mutations impact brain development in vivo and whether they have convergent or divergent effects on brain cellular architecture. To address this, we investigated cellular changes in the whole mouse brain of more than 20 different knock-out lines for high confidence NDD genes at postnatal day 14 and 2 months old. Brains underwent SHIELD based tissue clearing, 3D labeling to visualize neurons and microglia, followed by a light sheet microscopy imaging. We established a streamlined data processing pipeline to detect and quantify labeled signals across the whole brain, using custom built age- and modality-matching reference atlases for data integration and visualization. Our findings suggest that NDD risk genes differentially affect how cellular elements scale with underlying volume changes, to change cell type composition across brain regions. For example, *Fbn1* and *Cdkl5* knock-out lines both show increased brain region volumes at P56, but *Fbn1* mice show increased neuron counts that in many regions exceed the size increases, while *Cdkl5* mice generally show proportional or insufficient scaling in neuron numbers. The lines showing most prominent microglial reductions were *Magel2* and *Smarcc2*, both of which showed strong cerebellar phenotypes. Together, our results suggest that NDD risk genes can alter brain cellular architecture through distinct relationships between regional volume changes and cellular numbers, rather than through uniform changes in cell number alone.

Disclosures: I.E. Bjerke: None. **E. Han:** None. **N. Blaha:** None. **J. Pi:** None. **T. Leach:** None. **V. Kumar:** None. **Y. Kim:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.13/E2

Topic: A.06. Developmental Disorders

Support: Grants in Aid for Scientific Research (C) (24K11029) from the Japan Society for the Promotion of Science

Title: Targeting cortical hyperexcitability with phenytoin improves autism spectrum disorder-like phenotypes

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Abstract: Previously, we identified neocortical abnormalities characterized by altered cortical thickness resulting from changes in the number of projection neurons. These changes were caused by alterations in the probability of neural stem/progenitor cells exiting the cell cycle (Q fraction). Furthermore, we demonstrated that increased cortical thickness leads to autism spectrum disorder (ASD)-like phenotypes in vivo (Mitsuhashi et al., 2023). Because these phenotypes might be due to neocortical hyperexcitability, we investigated the effects of antiseizure medications as potential candidates for a drug-repositioning strategy. We used mice prenatally exposed to low-dose valproic acid (VPA) (Fujimura et al., 2016). Sodium channel blockers (phenytoin, carbamazepine, or lamotrigine) were orally administered to VPA-exposed mice (n = 79 males in total) and control mice (n = 126 males in total) for 4 weeks starting at 4 weeks of age. Traveled distance in open field test was assessed at 8 weeks of age, corresponding to young adulthood in mice. Phenytoin treatment significantly increased traveled distance in VPA-exposed mice compared with untreated VPA-exposed mice ($p = 0.013$). Moreover, no significant difference was observed between phenytoin-treated VPA-exposed mice and untreated control mice ($p = 0.509$), indicating normalization of open field activity. In contrast, carbamazepine and lamotrigine treatment failed to improve traveled distance in VPA-exposed mice compared with untreated VPA-exposed mice ($p = 0.114$ and $p = 0.747$, respectively). Perampanel has been proposed as a potential therapeutic agent for ASD. Therefore, we evaluated the effects of perampanel using the same treatment paradigm. However, perampanel treatment did not improve traveled distance in VPA-exposed mice compared with untreated VPA-exposed mice ($p = 0.867$). These findings suggest that phenytoin, but not carbamazepine, lamotrigine or perampanel, ameliorates abnormalities in the open field test in VPA-exposed mice. Moreover, the therapeutic effects observed with phenytoin may reflect mechanisms beyond a general reduction in cortical excitability.

Disclosures: T. Mitsuhashi: None. **F. Goto:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.14/E3

Topic: A.06. Developmental Disorders

Support: ASPIRE AARE-2020 (21M149)

Title: Zinc Homeostasis Shapes Gut Microbiota, Behavioral Phenotypes, and Colonic Architecture in an Autism Mouse Model: Evidence for a Narrow Therapeutic Window Along the Gut-Brain Axis

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Abstract: Autism spectrum disorder (ASD) has been linked to disruptions in zinc (Zn) homeostasis and gut microbial composition, both of which influence neurodevelopment, intestinal integrity, and behavior. However, the combined effects of Zn deficiency and excess on gut-brain axis function remain unclear. We investigated the longitudinal impact of dietary Zn modulation on behavior, microbiota, and gut histology in the BTBR T+Itpr3tf/J (BTBR) mouse model of ASD and C57BL/6J (B6) as controls. Eight-week-old male BTBR and B6 mice were maintained for 8 weeks on Zn-deficient (0 ppm), Zn-adequate (30 ppm), or Zn-excess (150 ppm) diets (n=8/group). Behavioral assessments were performed at baseline and weeks 4 and 8. Body weight and fecal samples were collected longitudinally for 16S rRNA sequencing, while colonic tissue and blood were analyzed at the endpoint. BTBR mice exhibited a more *Proteobacteria*-enriched and compositionally unstable microbiome than B6 controls. Longitudinal analyses revealed significantly greater microbial variability in BTBR mice, with Zn availability and time strongly influencing community structure. Alpha- and beta-diversity analyses demonstrated marked Zn- and time-dependent microbial shifts in BTBR mice, whereas B6 microbiota remained stable. Both, Zn deficiency and excess rapidly destabilized the BTBR microbiome, while B6 mice showed compositional resilience. Behavioral outcomes paralleled microbiome changes. BTBR mice displayed greater repetitive behaviors than B6 controls. Prolonged exposure to excess dietary Zn (150 ppm) exacerbated anxiety-like and repetitive behaviors in BTBR mice. While, BTBR mice fed a Zn-adequate diet exhibited progressive improvement in repetitive behaviors. Remarkably, Zn deficiency produced the most severe phenotype, causing critical weight loss and physiological deterioration requiring early humane euthanasia in BTBR mice, while B6 mice exhibited robust resilience across all dietary Zn levels. Histological analyses revealed strain- and Zn-dependent alterations in colonic architecture, including crypt abnormalities and increased neutrophilic infiltration under Zn deficiency. Collectively, these findings identify BTBR mice as particularly vulnerable to Zn dyshomeostasis and demonstrate that both Zn deficiency and excess disrupt gut brain axis function and exacerbate ASD-associated behavioral abnormalities. The data reveal a narrow physiological window for optimal Zn diet and suggest that maintaining Zn balance may represent a critical therapeutic strategy for mitigating ASD-associated microbial, metabolic, and behavioral dysfunction.

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Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.15/E4

Topic: A.06. Developmental Disorders

Support: iDREAM
Hawk-IDDRC
FamilieSCN2A Foundation
DOD

Title: Not All Nonsense: Allele-Specific Effects of Scn2a Nonsense Mutations on Transcriptional Compensation and Cerebellar Morphology

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Abstract: *SCN2A* encodes the alpha subunit of the voltage gated sodium channel $Na_V1.2$, which is necessary for action potential generation and propagation. Nonsense mutations in SCN2A are strongly associated with autism spectrum disorders (ASD) and intellectual disability. These mutations create a premature termination codon (PTC) in the reading frame of $Na_V1.2$ and are hypothesized to result in functional haploinsufficiency. In patients, multiple *SCN2A* PTCs have been Identified, yet whether distinct PTCs produce shared developmental phenotypes or compensatory changes in other sodium channel genes is unclear. $Na_V1.2$ is expressed in cerebellar granule neurons and may influence cerebellar cellular morphology. We used Nissl staining at the vermis of Y84X and R1627X mice cerebellums, aged P12 (n=12) and P21 (n=12), to measure cytoarchitectural features affected by $Na_V1.2$ loss during development. We also used quantitative polymerase chain reaction (qPCR) to evaluate potential transcriptional compensation from *Scn8a* mRNA which encodes $Na_V1.6$. $Na_V1.2$ and $Na_V1.6$ functionally overlap as voltage-gated sodium channels, co-expressed in excitatory glutamatergic neurons, that both support action potential initiation and propagation. We find that $Scn2a^{Y84X/+}$ P12 heterozygous (HET) mice show smaller Purkinje cell (PC) soma area than wild-type (WT) (WT-HET=25.8, p=0.0162) and lower PC density (WT-HET=0.293, p=0.0355). At P21, $Scn2a^{Y84X/+}$ PC soma area shows genotype by lobule by sex effects, with smaller soma in female lobule 2 (WT-HET=102.95, p=0.0003) and male lobule 6 (WT-HET=88.25, p=0.0009). $Scn2a^{Y84X/+}$ P21 mice also show lower PC density (WT-HET=0.394, p=0.0013). $Scn2a^{R1627X/+}$ P12 mice show sex-specific PC density differences in lobules 7, 9, and 10 (p= 0.0298, 0.0086, and 0.0446), but no P12 soma genotype effect. At P21, $Scn2a^{R1627X/+}$ mice show lower PC density (WT-HET=0.289,

p=0.0256) and a trend toward smaller soma area (WT-HET=18.2, p=0.0651). Preliminary qPCR data suggest that Scn8a mRNA is not increased in *Scn2a*$^{Y84X/+}$ brain at P7 (0.851 ± 0.07) n=6 or adult brain (0.829 ± 0.47) n=4 but is possibly elevated in *Scn2a*$^{R1627X/+}$ brain at P7 (1.310 ± 0.35) n=8 and adult brain (1.149 ± 0.32) n=4. Together, these findings suggest that *Scn2a*$^{Y84X/+}$ mice exhibit a more persistent disruption of cerebellar development, whereas *Scn2a*$^{R1627X/+}$ mice show a more restricted and potentially compensated developmental phenotype.

Disclosures: R.J. Gorter: None. **K. Scott:** None. **C. Ahern:** F. Consulting Fees (e.g., advisory boards); Tevard Bioscience. **A.J. Williams:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.16/E5

Topic: A.06. Developmental Disorders

Support: Research Council
MU Department of Radiology

Title: DHA Supplementation Rescues Volumetric and Behavioral Phenotypes in a Prenatal Stress ASD Mouse Model

Authors: *A. TOSH[1], N. I. AHMED[2], C. KING[3], J. ELLEGOOD[4], J. P. LERCH[5], M. J. WILL[6], D. Q. BEVERSDORF[7];
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Abstract: Autism spectrum disorder (ASD) pathogenesis includes gene-environment interactions. One example is prenatal stress exposure in the setting of maternal genetic stress susceptibility. We modeled human short-SERT allele stress vulnerability using heterozygous serotonin transporter knockout (SERT-het) mouse dams exposed to a perinatal chronic variable stress paradigm (including restraint, constant light, and novel noise) from embryonic day 6 to birth. Perinatal docosahexaenoic acid (DHA) supplementation or control diet was administered to 36 male offspring: stressed SERT-het on 1% DHA (HS/D, n = 9) or a control diet (HS/C, n = 9), and unstressed wild-type on 1% DHA (WN/D, n = 10) or a control diet (WN/C, n = 8). Diets were maintained from pre-mating through gestation, lactation, and post-weaning (in the offspring). Following behavioral assays at postnatal day 60 (PD60), ex vivo brains were harvested on PD70 for deformation-based morphometry using 7-Tesla MRI across 182 regions. Data were analyzed using a two-way factorial ANOVA (diet x group) followed by Tukey's HSD post-hoc tests. The maternal SERT-het stress model was significantly associated with absolute

total brain enlargement ($F(1,32) = 8.66$, $p = 0.006$), with significant expansion in cerebral gray matter (+5.86%, $p < 0.001$) and olfactory regions (+5.01%, $p = 0.001$). This enlargement extended to circuits associated with social motivation and repetitive behaviors, including the striatum/nucleus accumbens territory, claustrum, cingulate subregions, and cerebellar flocculus white matter. Furthermore, significant diet x group interaction effects were observed for the relative volumes of the claustrum ($F(1,35) = 9.71$, $p < 0.05$) and cingulate cortex area 24b ($F(1,35) = 6.57$, $p = 0.02$). HS/D absolute total volumes shifted significantly back toward the WN/C baseline ($p = 0.006$), completely rescuing 14 of 58 stress-affected individual regions, specifically restoring the amygdala, thalamus, claustrum, and anterior cingulate cortex, without altering wild-type volumes. Behaviorally, maternal DHA significantly increased time spent in social novelty ($F(1,35) = 4.43$, $p = 0.04$). Additionally, a statistically significant diet x group interaction effect for grooming frequency ($F(1,34) = 6.89$, $p = 0.01$) revealed that DHA selectively normalized the elevated grooming seen in the stress-model group without affecting wild-type controls, though baseline social preference deficits persisted. These results suggest that perinatal DHA selectively mitigates the volumetric changes induced by prenatal stress and the corresponding behaviors disrupted by gene-environment stressors.

Disclosures: A. Tosh: None. **N.I. Ahmed:** None. **C. King:** None. **J. Ellegood:** None. **J.P. Lerch:** None. **M.J. Will:** None. **D.Q. Beversdorf:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.17/E6

Topic: A.06. Developmental Disorders

Title: Sex Differences in Repetitive, Social, and Anxiety-Like Behaviors in BTBR Mice Following Sulforaphane Treatment

Authors: *M. CORSO[1], O. HOVER[1], O. CATALINA[1], S. FERNANDEZ[2], E. CRAIG[1], S. RIEBESELL[1], L. A. GABEL[1];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by deficits in social communication and the presence of restricted and repetitive behaviors. Although ASD arises from complex genetic and environmental influences, increasing evidence implicates oxidative stress, mitochondrial dysfunction, and impaired antioxidant defenses in its pathophysiology. The BTBR T+ Itpr3tf/J (BTBR) mouse strain is widely used as a model of idiopathic ASD because it exhibits elevated repetitive behaviors and has been reported to display impairments in social interaction. Sulforaphane (SFN), a naturally occurring compound derived from cruciferous vegetables, has demonstrated neuroprotective properties through its antioxidant and anti-inflammatory actions.In the present study, we examined the effects of SFN (50 mg/kg; oral self-administration) on ASD-relevant behaviors in 92 mice (45 C57BL/6J [BL6]; 47 BTBR).

Behavioral outcomes were evaluated using the marble burying test, open field test, elevated plus maze, and social interaction measures. Male and female BTBR mice exhibited significantly elevated repetitive behavior during marble burying compared with BL6 controls, and these behaviors were reduced following SFN treatment. Excessive grooming was also observed in BTBR mice, particularly in males, although SFN did not significantly alter grooming behavior. Sex-dependent effects of SFN were observed in the open field, where treated males displayed increased anxiety-like behavior relative to untreated controls.Consistent with previous reports, BTBR mice demonstrated robust and reproducible differences in repetitive behaviors. In contrast, deficits in sociability were not observed in the current cohort, and strain differences in anxiety-like behavior were less consistent across behavioral assays. These findings suggest that repetitive and compulsive-like behaviors may represent the most reliable behavioral phenotype of the BTBR strain under the conditions examined. While repetitive behaviors are a core feature of ASD, they are also characteristic of obsessive-compulsive disorder, raising important questions regarding the extent to which BTBR mice model distinct symptom domains across neurodevelopmental and psychiatric disorders.Overall, SFN selectively reduced marble-burying behavior but did not broadly improve other behavioral measures. Future studies comparing BTBR mice with genetically defined ASD models, including CNTNAP2 mutants, may help clarify the behavioral constructs captured by different models and improve the translational utility of preclinical studies of ASD and related disorders.

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Poster

PSTR297: Animal Models of Autism

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.18/E7

Topic: A.06. Developmental Disorders

Support: Autism Research Institute

Title: Maternal intravenous injection of prenatal-stress-related microRNA induces repetitive behaviors in C57Bl/6J offspring

Authors: *N. AHMED[1], O. L. SMITH[2], H. E. STEVENS[4], D. Q. BEVERSDORF[3];
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Abstract: The Developmental Origins of Health and Disease hypothesis (DoHaD) suggests that environmental stress exposure to the intrauterine and maternal systems at key developmental periods may lead to long-term impacts on the health of the offspring. Previous work in our lab has replicated a gene-by-environment (GxE) model of ASD where maternal SERT heterozygous

KO mice when exposed to chronic variable stress during pregnancy can result in autism-like phenotypes in the male offspring. We identified upregulated maternal miRNAs (mmu-miR-7684-3p, mmu-miR-5622-3p, mmu-miR-6900-3p) in this GxE model of ASD. To investigate the mechanistic role of the prenatal stress-associated miRNAs, these miRNA were replicated as oligonucleotide miRNA mimics and combined into a miRNA mix diluted to 50 ug/100 uL. C57Bl/6J pregnant mice were then injected with 100 uL of the GxE microRNA mimic, mis-sense RNA as a positive control, or sterile saline on gestational day 6 (G6) and again on G14. All groups were assessed at PD35 for developmental abnormalities using the acoustic startle response, olfactory and motor functioning, and neuromuscular ability. On postnatal day 60, offspring were behaviorally tested for social communication, repetitive behaviors, and other anxiety measures. No groups displayed differences in social communication. Offspring that were injected with any substance displayed jumping behaviors, but the GxE associated miRNA-exposed mice predominantly expressed jumping behavior in the direction of the walls of the apparatus while offspring injected with mis-sense or saline jumped upwards to the only exit of the apparatus. Behaviors also appeared sex specific as total jumping behaviors were highest in females of the GxE miRNA-injected offspring, but males displayed the most jumping in the two control injection groups. The miRNA-injected group also displayed altered anxiety profiles compared to both mis-sense and buffer-injected mice, including altered thigmotaxis during the open field and increased distance travelled in the elevated plus maze. These findings suggest maternal intravenous injection can produce altered behavioral profiles, but stress-related miRNAs may be capable of producing sex specific changes in some repetitive behaviors.

Disclosures: N. Ahmed: None. **O.L. Smith:** None. **H.E. Stevens:** None. **D.Q. Beversdorf:** F. Consulting Fees (e.g., advisory boards); YAMO Pharmaceuticals.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.19/E8

Topic: A.06. Developmental Disorders

Support: FAPESP 2022/15514-9

Title: Impact of prenatal exposure to valproic acid on Klotho levels and behavioral profile in male mice

Authors: *B. RODRIGUES;
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Abstract: Valproic acid (VPA) is a drug used to treat epilepsy. Prenatal VPA exposure is linked to an increased risk of congenital malformations and neurodevelopmental disorders, characterized by cognitive impairments, developmental delays, and an elevated prevalence of Autism Spectrum Disorder (ASD). The molecular basis of these alterations has yet to be fully

clarified, necessitating the exploration of candidates such as the Klotho protein as potential mediators, given its known neuroprotective role. The objective of this study was to investigate the effects of VPA on behavior, and Klotho protein expression in cognitive-related brain regions of male mice offspring exposed to VPA *in utero*. Pregnant female mice (C57/BL6) were treated with VPA (300 mg/kg) or saline on embryonic days 10 and 12. At one month old, male offspring (n=15) were subjected to behavioral tests: the Elevated Plus Maze (EPM), Social Interaction (SI), and Social Preference (SP) to evaluate anxiety-like behavior and social interaction. After the behavioral tests, a subset of the animals was euthanized, and their brains were removed for the dissection of the hippocampus, frontal cortex, and cerebellum. Total protein extraction was performed, and the samples were submitted to ELISA (n=5) to analyze soluble Klotho levels. The remaining animals were perfused and their brains were sectioned using a microtome for immunofluorescence (n=3) analysis to assess the spatial distribution of Klotho in cortical regions. Statistical analysis was performed using unpaired Student's T-Test, and Mann-Whitney in the GraphPad Prism. This study was approved by the Ethics Committee on the Use of Animals. In the EPM test, male VPA offspring showed an increase in time spent in the closed arms ($p=0.0147$), a reduction in time spent in the open arms ($p=0.0174$), and a reduction in the number of entries into the open arms ($p=0.0146$). No differences were observed in the number of entries into the closed arms. In the SI test, the VPA group showed reduced interaction with an unfamiliar animal ($p<0.0001$) but a significant increase in interaction with an object ($p=0.0010$). In the SP test, the VPA group exhibited increased interaction with a familiar animal ($p<0.0001$) and more time spent in the familiar animal's compartment ($p=0.0016$). Klotho levels were increased in the VPA group in the frontal cortex in ELISA ($p=0.0045$) and immunofluorescence ($p<0.0001$) assays. Our findings demonstrate anxiety-like phenotypes and altered social preference in male VPA. Additionally, the observed increase in frontal cortex Klotho expression suggests a possible compensatory response to prenatal VPA exposure. Financial support: FAPESP and CAPES.

Disclosures: B. Rodrigues: None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.20/F1

Topic: A.06. Developmental Disorders

Support: FC-PD2025
KO-SECITHI fellowship

Title: Dim blue light at night exacerbates circadian dysfunction, sleep architecture alterations, and social deficits in the C58/J mouse model of autism

Authors: K. OCAMPO ORTIZ[1], D. J. BUSTAMANTE VALDEZ[1], M. FUENTES-CANO[1], E. G. IBARRA CORONADO[2], ***P. DURAN**[1];
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Abstract: Autism spectrum disorder (ASD) is associated with social interaction impairments, repetitive/restrictive behaviors, sensory alterations, and sleep-wake cycle disturbances. Circadian synchronization depends on light signals detected by intrinsically photosensitive retinal ganglion cells and transmitted to the suprachiasmatic nucleus, the master circadian pacemaker regulating the sleep-wake cycle and locomotor activity, among other behaviors. Given the exposure to light during the scotophase -particularly short-wavelength light such as blue light- can act as a circadian disruptor, we evaluated the effect of dim blue light (8 lx) during the dark phase (DBLAN) on activity rhythms, social behavior, and sleep-wake cycle in C58/J mice (n=16), compared to C57BL/6 mice (n=16). Animals were inicially housed under a standard 12:12 LD cycle and subsequently shifted to a 12:12 LD DBLAN. Locomotor activity was recorded using infrared sensors, and actograms and circadian parameters (including period, phase, and amplitude) were analyzed. Social behavior was assessed using the three-chamber social interaction test between ZT14 and ZT18. The sleep-wake cycle was quantified via 48-h ECoG recordings (C57BL/6 n=4; C58/J n=4), to classify Wake, NREM, and REM sleep. Under standard 12:12 LD conditions, C58/J mice exhibited a shortened activity period, a delay in the active phase onset (α), and an advance in the rest phase (ρ) compared to C57BL/6 mice. DBLAN induced a further delay of α, a reduction in locomotor rhythm amplitude, and actograms displaying free-running-like characteristics followed by abrupt resynchronization. Strain differences were also observed in social interaction and sleep architecture: under standard 12:12 LD conditions, REM sleep percentages varied between strains, and under DBLAN exposure, the overall composition of the sleep-wake cycle was modified. These results suggest that dim blue light during the scotophase exacerbates circadian vulnerability in C58/J mice and is associated with alterations in locomotor activity, social behavior, and sleep-wake organization.

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Poster

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.21/F2

Topic: A.06. Developmental Disorders

Support: NIH
Simons Foundation

Title: Defining mechanisms of TBR1 Syndrome using diverse allelic variants

Authors: *M. CO[1], K. PATTON[2], G. O'BRIEN[2], K. WRIGHT[3], B. J. O'ROAK[2];
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Abstract: *De novo* heterozygous *TBR1* variants cause TBR1 Syndrome, a complex neurodevelopmental disorder characterized by intellectual disability, autism or autistic features, and behavioral challenges. Pathogenic *TBR1* coding variants vary in their type (e.g., frameshift, nonsense, missense) and genomic location (exon 1-6), but how these attributes impact gene function and downstream phenotypes is not fully elucidated. We used CRISPR to generate novel mouse alleles representing three predicted *TBR1* variant types: (1) "early-terminating" leading to loss-of-function via nonsense-mediated decay (NMD), (2) missense clustered in the T-box DNA-binding domain, and (3) "late-terminating" predicted to escape NMD and alter the C-terminal domain, potentially contributing to more severe outcomes reported by clinicians and parents. Using molecular, biochemical, genomic, and behavioral approaches, we discovered overlapping and allele-specific impacts *in vivo*. We observed a wide range of impacts on TBR1 protein abundance in postnatal cortex, from complete loss of protein to ~5-fold increase among homozygotes. Alleles also differentially impacted CTIP2+ neuron distributions across cortical layers in homozygotes. Allelic impacts converged on axon developmental processes, with heterozygotes phenocopying reductions in anterior commissure thickness seen in human TBR1 Syndrome. Additional analyses using a hypomorphic *Tbr1* allele revealed particular sensitivity of the anterior commissure to slight reductions in TBR1 dosage. Using RNA-seq, we found that *Tbr1* knockout, early-terminating, and T-box missense alleles all impacted gene programs for heparan sulfate 3-O-sulfation and neurofilament expression in embryonic cortex. Ongoing single-cell RNA-seq analysis will query the neuronal subtype specificity of *Tbr1* allelic impacts in embryonic neocortex and paleocortex. Last, *Tbr1* heterozygotes showed differences in ambulatory behavior at postnatal day 10 in an allele-dependent manner. Future work will investigate how variations in TBR1 protein sequence and protein dosage impact biochemical interactions and neuronal development. Findings will contribute to our fundamental understanding of brain development as well as inform treatment approaches for monogenic disorders driven by diverse variants.

Disclosures: M. Co: None. **K. Patton:** None. **G. O'Brien:** None. **K. Wright:** None. **B.J. O'Roak:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.22/F3

Topic: A.06. Developmental Disorders

Support: Beckman Institute Seed Grant
Biomedical Imaging Center at Beckman Institute

Title: Cell-Type-Specific Loss of FMRP Differentially Disrupts Social, Anxiety-Related, and Sensory Behaviors in Mouse Models of Fragile X Syndrome

Authors: *L. MITCHELL[1], H. WANG[3], Z. KUANG[1], J. BENSON[5], J. GOENSE[1], B. D. AUERBACH[4], H. GRITTON[2];
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Abstract: Fragile X syndrome (FXS) is the leading inherited cause of autism spectrum disorders (ASD) and results from transcriptional silencing of the *Fmr1* gene, leading to loss of Fragile X Messenger Ribonucleoprotein (FMRP). Disrupted excitatory-inhibitory (E-I) balance has emerged as a canonical circuit deficit in FXS and ASD and has been proposed to contribute to diverse behavioral phenotypes. Although E/I imbalance is widely implicated in ASD pathophysiology, the relative contributions of excitatory and inhibitory neuronal populations to behavioral dysfunction remain unclear. We tested whether selective loss of FMRP within distinct neuronal populations is sufficient to produce core ASD-relevant phenotypes present in global Fmr1-KOs. Conditional *Fmr1* knockout (cKO) mice were generated using Cre-loxP strategies to selectively delete *Fmr1* from either parvalbumin-expressing (PV) inhibitory interneurons or CaMKIIα-expressing excitatory neurons. Mice were evaluated using a behavioral battery assessing core phenotypes observed in ASD, including social interaction, anxiety-like behavior, locomotor activity, and sensory processing. Social behavior was measured using the three-chamber social interaction test, anxiety-related behaviors were assessed in the open field and elevated plus maze, and sensory processing abnormalities were evaluated using acoustic startle testing. Conditional deletion of *Fmr1* in excitatory (CaMKIIα-cKO) or inhibitory (PV-cKO) populations recapitulated some of the phenotypes observed in global Fmr1-KOs, while failing to reproduce others, ultimately resulting in overlapping but distinct behavioral profiles. These results support a model in which cell-type specific circuit dysfunction contributes to behavioral phenotypes in FXS and provide insight into how disruption of *Fmr1* expression alters neural circuit function to drive ASD-related behaviors.

Disclosures: L. Mitchell: None. **H. Wang:** None. **Z. Kuang:** None. **J. Goense:** None. **B.D. Auerbach:** None. **H. Gritton:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.23/F4

Topic: A.06. Developmental Disorders

Support: Beckman Institute Seed Grant

Title: Sensory distractors destabilize perceptual decision-making associated with altered attentional state control in a mouse model of Fragile X Syndrome

Authors: *R. BELL[1], L. MITCHELL[2], M. IRANI[3], C.-F. SUN[5], H. GRITTON[4];
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Abstract: Atypical sensory processing is a core feature of autism spectrum disorders (ASD), yet the circuit and cognitive mechanisms underlying sensory dysfunction remain poorly understood. Individuals with ASD frequently report difficulty processing sensory information in complex environments, raising the question of whether these abnormalities arise from impaired sensory encoding or disrupted attentional control over competing stimuli. Fragile X syndrome (FXS), the leading inherited cause of ASD, provides a valuable model for investigating the neural basis of sensory processing deficits. We tested Fmr1 knockout (KO) mice, a well-established model of FXS, and wild-type (WT) littermates on an auditory discrimination task designed to dissociate sensory perception from attentional demands. Mice were trained on a two-alternative choice task requiring discrimination among seven tones spanning two octaves under quiet conditions or in the presence of auditory and visual distractors that increased perceptual load. Behavioral performance was analyzed using both psychometric modeling and a Generalized Linear Model-Hidden Markov Model (GLM-HMM) frameworks to assess perceptual sensitivity and latent behavioral states. Under simple listening conditions, KO mice exhibited intact auditory discrimination comparable to WT controls. However, when distractors were introduced, KO mice displayed marked impairments in performance, indicating increased vulnerability to competing sensory information both within-modality and in cross-modal contexts. Computational modeling revealed that these deficits could not be explained by impaired sensory encoding alone but instead reflected altered behavioral strategies and reduced attentional control under conditions of increased perceptual demand. These findings support a model in which sensory dysfunction in FXS arises in part from impaired top-down regulation and filtering of competing inputs rather than primary deficits in sensory perception. More broadly, the results suggest that auditory hypersensitivity in ASD may reflect a failure of attentional modulation, leading to impaired perception in complex sensory environments. By dissociating sensory encoding from attentional control, this work provides new insight into the mechanisms underlying sensory processing abnormalities in ASD.

Disclosures: R. Bell: None. **L. Mitchell:** None. **M. Irani:** None. **C. Sun:** None. **H. Gritton:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.24/F5

Topic: A.06. Developmental Disorders

Support: Beckman Institute Seed Grant
Biomedical Imaging Center at Beckman Institute

Title: MRI functional connectivity changes associated with cell-specific loss of FMRP in mouse models of Fragile X Syndrome

Authors: *Z. KUANG[1], J. BENSON[1], L. MITCHELL[1], H. WANG[3], B. D. AUERBACH[4], H. GRITTON[2], J. GOENSE[1];
[2]Comparative Biosci., [1]Univ. of Illinois, Urbana, IL; [3]Univ. of Illinois Urbana-Champaign, Champaign, IL; [4]Mol. & Integrative Physiol., Univ. of Illinois Urbana-Champaign, URBANA, IL

Abstract: Fragile X syndrome (FXS) is the leading monogenetic cause of autism spectrum disorder (ASD) and results from a loss-of-function mutation in the FMR1 gene and subsequent loss of Fragile X Messenger Ribonucleoprotein (FMRP). Disruption of the excitatory-inhibitory (E-I) balance is a hallmark of FXS and has been proposed to contribute to widespread abnormalities in neural circuit function. Resting-state functional magnetic resonance imaging (rs-fMRI) studies in global Fmr1 knockout mice have revealed altered functional connectivity (FC), particularly within networks implicated in social behavior and the modulation of repetitive behaviors. However, the mechanisms underlying these network-level abnormalities remain poorly understood. We used high-resolution resting-state fMRI to determine whether selective loss of FMRP in distinct neuronal populations is sufficient to produce circuit-level connectivity abnormalities. Functional connectivity was assessed in male global Fmr1 knockout mice (KO), conditional KO mice lacking Fmr1 in parvalbumin-expressing inhibitory interneurons (cKO-PV), conditional KO mice lacking Fmr1 in CaMKII-positive excitatory neurons (cKO-CaMKII), and wild-type controls (WT). Whole-brain network analysis and region-of-interest (ROI) pairwise connectivity measures were used to characterize both global and circuit-specific alterations. Consistent with previous reports, global KO mice exhibited widespread hyperconnectivity relative to WT controls, and increased FC across circuits associated with social memory, anxiety, and affective processing. Notably, both conditional knockout models displayed greater divergence from WT connectivity patterns than global KO animals at the whole-brain network level, indicating pronounced disruptions in large-scale functional organization. Moreover, selective deletion of Fmr1 from excitatory versus inhibitory neuronal populations produced distinct circuit-level connectivity signatures, characterized by unique patterns of local network disruption and long-range connectivity alterations. These findings demonstrate that cell-type-specific loss of FMRP is sufficient to drive widespread functional network abnormalities and reveal differential contributions of excitatory and inhibitory neuronal populations to circuit dysfunction in FXS. Together, these results provide new insights into the cellular origins of network pathology and advance our understanding of how disrupted Fmr1 expression alters brain-wide connectivity to contribute to ASD-related phenotypes.

Disclosures: Z. Kuang: None. **J. Benson:** None. **L. Mitchell:** None. **H. Wang:** None. **B.D. Auerbach:** None. **H. Gritton:** None. **J. Goense:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.25/F6

Topic: A.06. Developmental Disorders

Support: NIH Grant NS106244
NIH Grant EY022730

Title: Developmental Alterations of Cortical Oscillations in Mouse Models of Autism: Is the Thalamic Reticular Nucleus Responsible?

Authors: *R. HERRERA-MOLINA[1], M. T. COLONNESE[2];
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Abstract: Alterations in inhibitory circuits are common across autism. In mouse models of autism, both hypo- and hyper-activity of the thalamic reticular nucleus (TRN) -the primary source of inhibition to thalamocortical relay nuclei-generates autism-related thalamocortical circuit endophenotypes. The developing TRN is an attractive but understudied early target for autism-related genes. Our work in neonatal mouse visual cortex demonstrates that TRN is essential for the generation of spontaneous oscillations, called spindle bursts, and also for the refinement of thalamocortical projections. Because it is interconnected with all thalamic (and therefore cortical) regions, we hypothesized that TRN dysfunction during development has critical consequences for thalamocortical circuit function and may result in early autism-related circuit endophenotypes. As an initial step to test our hypothesis, we show here that oscillatory activity in the visual cortex is reduced in pups from mutant mouse models lacking the expression of the transmembrane glycoprotein Neuroplastin (Nptn), a novel autism-related gene. Compared with control $Nptn^{lox/lox}$ littermates, conditional pups lacking *Nptn* in GAD2 (+) inhibitory neurons ($Nptn^{lox/loxGad2Cre}$) or only in Parvalbumin (+) TRN neurons ($Nptn^{lox/loxPvalbCre}$) display drastically reduced occurrence of spindle-bursts and corresponding drop in the power of spindle frequencies in the local field potential, pointing to altered thalamic input activity at P6-P8. Interestingly, $Nptn^{lox/loxGad2Cre}$ pups had reduced cortical firing and low synchronization of the L2/3-L4 firing with the oscillations in L4 LFP, suggesting additional cortical circuitry regulation by local cortical interneurons. Because Nptn is an auxiliary subunit essential for the expression of the Plasma Membrane Ca^{2+} ATPases (PMCAs), we propose that Nptn-PMCA function is required by TRN neurons to promote the development of CT circuits. Currently, this idea and the potential susceptibility of the developmental TRN to autism-related circuit activity dysregulation in mouse models of autism are under investigation.

Disclosures: R. Herrera-Molina: None. **M.T. Colonnese:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.26/F7

Topic: A.06. Developmental Disorders

Support: SECIHTI 2012996

Title: Neuromodulation of Social Behavior and E/I Balance via Low-Frequency rTMS in an ASD Mouse Model

Authors: *V. I. PASTRAN[1], E. G. IBARRA CORONADO[2], L. VERDUGO-DIAZ[3];
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[3]Univ. Nacional Autonoma Mexico, Ciudad de México, Mexico

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication, repetitive behaviors, and alterations in the excitatory/inhibitory (E/I) balance of neural circuits. Glutamate and gamma-aminobutyric acid (GABA), the primary excitatory and inhibitory neurotransmitters in the central nervous system, are heavily implicated in ASD pathophysiology. Although repetitive Transcranial Magnetic Stimulation (rTMS) has emerged as a promising non-invasive neuromodulatory technique capable of modifying neuronal activity and network organization, its precise effects on E/I balance and behavioral outcomes in ASD remain poorly understood.This study evaluated the effects of low-frequency rTMS on social behavior and neurochemical markers of E/I balance in C58/J mice, an inbred model exhibiting autism-like phenotypes. Mice received daily low-frequency rTMS (1 Hz, 10 min/session) targeted to the motor cortex for 15 consecutive days using a dedicated small-animal figure-eight coil. Magnetic resonance spectroscopy (MRS) was performed before and after the intervention to quantify glutamate and GABA levels. Behavioral changes were evaluated using standard social interaction paradigms.Following treatment, C58/J mice exhibited increased social recognition, demonstrated by prolonged sniffing behavior during social testing, which suggests enhanced social motivation. Parallel MRS measurements successfully quantified treatment-induced changes in excitatory and inhibitory neurotransmitter markers, establishing a clear baseline relationship between neurochemical shifts and behavioral outcomes.Together, these findings demonstrate the potential of rTMS to ameliorate social deficits in an ASD mouse model and provide a robust framework for investigating the neurobiological mechanisms underlying neuromodulation. Characterizing the relationship between behavioral recovery and shifts in glutamatergic and GABAergic markers may facilitate the development of targeted, non-invasive therapeutic strategies aimed at restoring E/I homeostasis in ASD.

Disclosures: V.I. Pastran: None. **E.G. Ibarra Coronado:** None. **L. Verdugo-Diaz:** None.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.27/F8

Topic: A.01. Neurogenesis and Gliogenesis

Title: Development and Optimization of PSC-Derived Neuron-Astrocyte Co-Culture Models Using a Physiologically Relevant Basal Medium

Authors: *M. A. DERR[1], A. IBRAHIMI[2], K. LAHA[3], D. KUNINGER[1], S. SHIN[2];
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Abstract: Human pluripotent stem cell (PSC)-derived neural cultures are increasingly utilized as New Approach Methodologies (NAMs) for studying neurobiology, modeling disease, and evaluating therapeutic candidates. The predictive value of these models depends on their ability to recapitulate key aspects of human brain physiology, including neuronal excitability, synaptic communication, and neuron-glia interactions. However, many commonly used neuronal culture media contain nutrient and metabolite concentrations that differ substantially from those found in the central nervous system. These non-physiological conditions can alter cellular metabolism and neuronal activity, potentially limiting the relevance of in vitro findings. While physiologically relevant media have been developed to better mimic the brain extracellular environment, some formulations can compromise cell survival and long-term culture performance. Therefore, there remains a need for culture media that support physiologically relevant cellular activity while maintaining robust neuronal health. Here, we present the development and optimization of PSC-derived neuron-astrocyte co-culture models using a novel physiologically relevant basal medium designed to more closely replicate the metabolic composition of the brain extracellular milieu. Optimization studies evaluated neuronal and astrocyte survival, cellular morphology, neurite outgrowth, and development and maintenance of neuronal activity. Additional studies assessed compatibility with established neuronal culture workflows and the ability to support functionally relevant neuronal networks. Results demonstrate that the novel medium supports high levels of neuronal and astrocytic survival while enabling the establishment of stable co-cultures suitable for downstream applications. Importantly, the medium maintains physiological relevance without sacrificing the robust culture performance required for routine experimental use. Ongoing studies are focused on defining optimal culture conditions and characterizing the impact of the medium on neuronal maturation and network activity. Collectively, these findings demonstrate that physiologically relevant culture conditions can be achieved without compromising survival or experimental robustness in PSC-derived neuron-astrocyte co-culture systems. By supporting both cellular health and physiologically relevant neuronal function, this medium has the potential to improve the biological fidelity and translational value of human in vitro neural models, further enabling the adoption of NAMs in neuroscience research and drug development.

Disclosures: M.A. Derr: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **A. Ibrahimi:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **K. Laha:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **D. Kuninger:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **S. Shin:** A. Employment/Salary (full or part-time):; Employment, Thermo Fisher Scientific.

Poster

PSTR297: Animal Models of Autism

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR297.28/G1

Topic: A.01. Neurogenesis and Gliogenesis

Support: R21AG085052-01A1
UC Start-up funds to Liaudanskaya
University Research Scholar Award

Title: Multicellular Brain Models Reveal Neurodevelopmental Programs that Converge with Autism

Authors: S. STERBEN[1], C. ANAMALA[1], S. KANSAKAR[1], ***V. LIAUDANSKAYA**[2]; [1]Biomed. Engin., [2]Biomed. Engin. and Neurosci. Grad. Program, Univ. of Cincinnati, Cincinnati, OH

Abstract: Neuronal maturation takes place within a multicellular environment where astrocytes and microglia support development through extracellular matrix remodeling, immune signaling, metabolic regulation, and synapse formation. Although altered glial function has been implicated in autism spectrum disorder (ASD), it remains unclear how specific glial populations shape human neuronal maturation and contribute to ASD-associated molecular states.
Here, we employed a series of progressively complex 3D human cell-derived brain culture models consisting of neurons alone, neuron-microglia co-cultures (NM), neuron-astrocyte-microglia cultures (NAM), and neurovascular multicellular cultures (PENTA) to define cell-specific developmental support programs during human neuronal maturation. Transcriptomic profiling revealed that increasing cellular complexity induced distinct extracellular matrix, immune, cytokine, and metabolic support pathways. Microglia preferentially promoted complement and inflammatory signaling, whereas astrocytes enhanced extracellular matrix remodeling and developmental support programs. Neurovascular cells further expanded the extracellular matrix, adhesion, and vascular-associated pathways.To determine the relevance of these developmental programs to neurodevelopmental disease, we compared culture-specific transcriptomic signatures with published ASD cortical datasets. Neuron-only cultures demonstrated minimal overlap with ASD-associated transcriptional alterations, whereas multicellular cultures showed substantial convergence with ASD-associated extracellular matrix, inflammatory, and glial-support signatures. In contrast, neuronal maturation, synaptic organization, calcium signaling, and mitochondrial pathways diverged from ASD signatures, suggesting that glial developmental programs represent a major point of ASD convergence. Thus, our data identify glial developmental programs as a major source of transcriptomic convergence with ASD. ASD-associated signatures were largely absent in neuron-only cultures and emerged progressively with increasing cellular complexity, suggesting that multicellular interactions are a key driver of ASD-associated molecular states. These findings support a model in which diverse ASD risk factors converge on common developmental support pathways.

Disclosures: S. Sterben: None. **C. Anamala:** None. **S. Kansakar:** None. **V. Liaudanskaya:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.01/G2

Topic: A.10. Schizophrenia

Support: NIH Grant 30038341
MSCRF

Title: Effects of SETD1A Haploinsufficiency in Human Cerebellar Organoids

Authors: *A. CHANDIA CRISTI[1,2,3,4], S. BARLOW[1,4,5], S. P. ARJONA[1,2,3,4], M. E. CORTES-GUTIERREZ[1,2,3,4], T. A. BLANPIED[1,4,5], S. A. AMENT[1,2,3,4];
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Abstract: The human cerebellum is involved in various neurological and psychiatric diseases, including schizophrenia (SCZ). Several line of the evidence suggest that Purkinje cells, the main output neurons of the cerebellar cortex, are altered in SCZ. Postmortem studies have reported reductions in Purkinje cell size and density. Transcriptomic analyses have identified downregulated gene networks related to synaptic function in Purkinje cell dendrites. Furthermore, developmental cell-atlas and single-cell sequencing studies show that many SCZ risk genes are preferentially expressed in Purkinje cells during pre- and postnatal development. Together, these findings support a role for Purkinje cell dysfunction in the pathophysiology of SCZ. However, few studies have tested the causal effects of mutations associated with risk for SCZ on the development of Purkinje cells, and almost none have investigated effects in human Purkinje cells. Rare, heterozygous loss-of-function variants in *SETD1A,* a histone methyltransferase, are associated with >10-fold increased risk for SCZ. Therefore, we hypothesized that S*ETD1A* haploinsufficiency would cause defects in Purkinje cell development, mirroring those observed in SCZ patients. To investigate cerebellar neurodevelopmental alterations, we implemented a protocol to generate three-dimensional human cerebellar organoids (hCerOs) from induced pluripotent stem cells (iPSC), comparing genome-editing heterozygous loss-of-function *SETD1A* iPSC to isogenic controls. Immunostaining indicated that six-month-old hCerOs of both genotypes contain a high proportion contain a high proportion of Purkinje cell and granular cells with morphologically mature excitatory synapses. We are using these resources and technologies to model the impact of *SETD1A* haploinsuffiency on cerebellar development.

Disclosures: A. Chandia Cristi: None. **S. Barlow:** None. **S.P. Arjona:** None. **M.E. Cortes-Gutierrez:** None. **T.A. Blanpied:** None. **S.A. Ament:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.02/G3

Topic: A.10. Schizophrenia

Title: Cerebellar morphology changes in a mouse model for the neurodevelopmental disorder-associated 3q29 deletion

Authors: *E. ARNULFO CANDELARIO[1,2], M. KRETZER[1], R. PURCELL[1,2], M. VAN DER HEIJDEN[1,2];
[1]Fralin Biomed. Res. Inst., Virginia Tech., Roanoke, VA; [2]Col. of Science, Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: The 3q29 deletion (3q29Del) is a copy number variant associated with a high risk for schizophrenia and autism spectrum disorder, among other neuropsychiatric conditions. Many individuals with 3q29Del also experience neurodevelopmental delays related to speech and motor control, but the neurobiological basis for these phenotypes remains unknown. Recent studies have reported decreased cerebellar volume in individuals with 3q29Del, and this structural difference is associated with the severity of the cognitive and behavioral phenotype. The cerebellum is involved in motor control and higher cognitive functions.
We set out to test whether mice with the homologous 3q29Del recapitulate the smaller cerebellum observed in human carriers. We immunostained at least three sections for each cerebellar region (vermis, paravermis, and hemisphere) in control and 3q29Del mice (N = 3/genotype). Cerebellum surface area, Purkinje cell density, and layer surface area were quantified. The surface area analysis suggests that compared to controls, mice with the homologous 3q29Del exhibit reduced cerebellar surface area in the vermis ($p=0.0363$), paravermis ($p=0.0207$), and hemisphere ($p=0.0095$) as observed in individuals with 3q29Del. However, these differences are not due to Purkinje cell density. We then subdivided the vermis and paravermis into anterior, central, and posterior regions for molecular and granule cell layer surface area analyses. These analyses showed a smaller surface area in the molecular layer of the central vermis ($p=0.0082$) between genotypes. This suggests that the layer surface area and other cerebellar structures contribute to the difference in cerebellar volume. Future directions will further examine the surface areas of the molecular and granule cell layers of the cerebellum to determine which layers and cell types contribute to the observed smaller cerebellar size. Along with investigating differential gene and protein expression to determine molecular determinants of this phenotype. The observed smaller cerebellar surface area in 3q29Del mice supports the possibility of leveraging this mouse model to investigate cerebellar phenotypes and better understand how it contributes to 3q29Del-associated neurodevelopmental disorders.

Disclosures: E. Arnulfo Candelario: None. **M. Kretzer:** None. **R. Purcell:** None. **M. van der Heijden:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.03/G4

Topic: A.10. Schizophrenia

Support: Canadian Institutes of Health Research
SECIHTI

Title: Dendritic spine degeneration in thalamic reticular nucleus neurons in the neonatal ventral hippocampal lesion model of schizophrenia

Authors: *H. TENDILLA-BELTRÁN[1], D. APAM-CASTILLEJOS[2], H. EDWARDS[3], V. M. MAGDALENO-MADRIGAL[4], J. S. NACHER[5], G. FLORES[2], L. K. SRIVASTAVA[6]; [1]Cinvestav, San Felipe Ixtacuixtla, Mexico; [2]Univ. Autonoma de Puebla / Inst. de Fisiologia, Puebla, Mexico; [3]Toronto Metropolitan Univ., Toronto, ON, Canada; [4]Inst. Nacional De Psiquiatría Ramón de la Fuente Muñiz, Ciudad De México, Mexico; [5]Univ. Valencia Esq4618001d, Burjassot, Spain; [6]McGill Univ., Douglas Hosp. Res. Ctr., Montreal, QC, Canada

Abstract: Schizophrenia (SZ) is a neurodevelopmental disorder in which excessive synaptic pruning is thought to contribute to cortical dysfunction. The thalamic reticular nucleus (TRN), a key regulator of thalamo-cortical information flow, may also be affected by these pathological processes; however, structural alterations of TRN neurons in SZ remain poorly understood. We hypothesized that TRN neurons exhibit structural abnormalities in the neonatal ventral hippocampal lesion (NVHL) rat, a well-established neurodevelopmental model of SZ in which early-life disruption of prefrontal cortex-hippocampal circuitry leads to widespread neural circuit and behavioral abnormalities resembling core features of the disorder. Notably, the NVHL model exhibits evidence of excessive synaptic pruning, manifested as dendritic spine degeneration characterized by reduced spine density and a decreased proportion of mature mushroom spines in corticolimbic regions. To determine whether similar alterations occur in the TRN, dendritic spine morphology and parvalbumin (PV)-positive cell density were evaluated in adult NVHL rats. NVHL animals exhibited a dendritic spine degeneration in TRN neurons, accompanied by a significant reduction in PV-positive cell density. These findings demonstrate profound structural alterations of TRN neurons in the NVHL model and suggest that excessive synaptic pruning extends to thalamic inhibitory networks. Given the critical role of PV neurons in regulating TRN excitability and synchronizing thalamo-cortical activity, their loss may disrupt the local excitation-inhibition balance, leading to impaired sensory gating and aberrant information processing. Collectively, these results identify the TRN as a potential substrate linking aberrant neurodevelopmental processes to thalamo-cortical and cortico-limbic dysfunction in SZ.

Disclosures: H. Tendilla-Beltrán: None. **D. Apam-Castillejos:** None. **H. Edwards:** None. **V.M. Magdaleno-Madrigal:** None. **J.S. Nacher:** None. **G. Flores:** None. **L.K. Srivastava:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.04/H1

Topic: A.10. Schizophrenia

Support: Abramson Fund
ABCD Charitable Trust
Larian Fund

Title: Postnatal loss of Cul1 in forebrain pyramidal neurons causes neurodegeneration with behavioral and circadian abnormalities

Authors: *H. JAARO-PELED, V. SUSHEER, H. EDUPUGANTI, Q. LIU, M. WU, R. L. MARGOLIS;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Background *CUL1* was identified by the SCHEMA consortium as harboring rare protein truncating variants that confer high risk for the development of schizophrenia. *CUL1* mutations have also recently been identified as causing congenital neurodevelopmental disorders characterized by microcephaly and intellectual impairment. CUL1 is a scaffolding component of the SCF E3 ubiquitin protein ligase complex which mediates the ubiquitination and degradation of various substrates, including circadian cycle regulators. We therefore hypothesized that neuronal loss of Cul1 will stabilize SCF substrates, leading to impaired proteostasis with detrimental effects on brain, behavior and circadian rhythms.
Methods Floxed *Cul1* conditional knockout mouse were generated and crossed with αCaMK-Cre transgenic mice, leading to postnatal deletion of Cul1 from forebrain excitatory pyramidal neurons. We compared Cre-positive littermates homozygous (Hom) or heterozygous (Het) for Cul1 loss to WT mice. Females and male mice were tested separately, and the results were combined if sex differences were not found. Analyses were done blinded to genotype.
Results Hom mice are smaller than WT/ Het mice from 3 months onward, and ~30% die prematurely. By 1 year Hom brains are smaller with massive brain atrophy, enlarged lateral ventricles, thinner corpus callosum, thinner cortex, and disordered cortical layers. Using Gfap and Iba1 markers we detected astrocytosis and microgliosis by 3 months of age. Bulk RNA-seq of the frontal cortex at 3 months highlighted downregulation of synaptic pathways and upregulation of integrated stress response (ISR) markers and innate immune pathways. 24 h open field testing revealed that Hom are hyperactive, are atypically active towards the end of the dark phase and avoid the center. Wheel running experiments under constant darkness uncovered longer circadian period and lower circadian amplitude. Cortical levels of circadian regulators Cry1 and Cry2 were also altered in Hom. The transcript levels of circadian regulators were downregulated in Hom.
Conclusions Homozygous, but not heterozygous, loss of Cul1 in forebrain pyramidal neurons postnatally causes robust alterations in molecular signature, including activation of the ISR and

innate immunity; neurodegeneration; hyperactivity and avoidance of center in open field testing; and altered circadian rhythms. These results strongly suggest that CUL1 is essential to forebrain pyramidal neuron survival and provides insight into the consequences of CUL1 loss in human patients with schizophrenia or neurodevelopmental abnormalities.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.05/H2

Topic: A.10. Schizophrenia

Support: Stanley Family Foundation

Title: Altered Expression of Interneuron-Related Genes and Inhibitory Neuronal Function in Zmym2 Mutant Mice, a Genetic Model of Schizophrenia and Neurodevelopmental Disorders

Authors: *W.-C. HUANG[1], H. GANGAL[5], S. ARYAL[2], N. GOBLE[6], Y. GE[9], A. HALL[7], A. ASAN[8], Y. WANG[1], P. S. KUNWAR[10], J. Q. PAN[3], A. J. GRANGER[4], M. H. SHENG[11]; [2]Stanley Ctr. for Psychiatric Res., [1]Broad Inst., Cambridge, MA; [3]Stanley Ctr. for Psychiatric Res., Broad Inst., Acton, MA; [4]Stanley Ctr., Broad Inst., Boston, MA; [5]Neurosci., Broad Inst. of MIT and Harvard, Cambridge, MA; [6]Broad Inst. of MIT and Harvard, Boston, MA; [7]Stanley Ctr. for Psychiatric Res., [8]Broad Inst. of MIT and Harvard, Cambridge, MA; [9]Univ. of British Columbia, West Vancouver, BC, Canada; [10]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT & Harvard, Cambridge, MA; [11]Neurosci. Res., Genentech Inc., South San Francisco, CA

Abstract: Schizophrenia (SCZ) is a severe psychiatric disorder affecting approximately 1% of the population. Although its underlying mechanisms remain incompletely understood, major hypotheses implicate dopaminergic dysregulation and dysfunction of interneurons. Predicted loss-of-function mutations in *ZMYM2* have been associated with increased risk for SCZ, neurodevelopmental disorders, and obsessive-compulsive disorder. ZMYM2 interacts with epigenetic regulatory complexes that control gene expression; however, how reduced ZMYM2 function affects brain molecular and physiological processes remains unclear. In this study, we found that heterozygous loss of *Zmym2* reduced RNA and protein levels of interneuron-related genes, including *Gad1* and *Pvalb*, consistent with patterns reported in SCZ postmortem brain studies. Histological analyses further supported reduced GABAergic interneuron-related signals in 3-month-old $Zmym2^{+/-}$ mice. To determine the functional consequences of these molecular and cellular changes, we performed electrophysiology and EEG analyses. $Zmym2^{+/-}$ mice showed reduced sIPSC frequency and altered low-frequency oscillatory activity, indicating impaired inhibitory circuit function. Behaviorally, $Zmym2^{+/-}$ mice showed an enhanced locomotor response to amphetamine and impaired sensory gating. Together, these findings

suggest that reduced ZMYM2 function affects interneuron-related gene expression and neural network activity. The *Zmym2* mutant mouse provides a genetically relevant model for investigating molecular and circuit mechanisms related to SCZ and associated neuropsychiatric disorders.

Disclosures: W. Huang: None. **H. Gangal:** None. **S. Aryal:** None. **N. Goble:** None. **Y. Ge:** None. **A. Hall:** None. **A. Asan:** None. **Y. Wang:** None. **P.S. Kunwar:** None. **J.Q. Pan:** None. **A.J. Granger:** None. **M.H. Sheng:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Topic: A.10. Schizophrenia

Support: NIH Grant MH118298
NIH Grant MH131717

Title: Neurogranin and GluN2A Haploinsufficiency Converge on Dendritic Spine Loss and Impaired Binocular Depth Perception in Visual Cortex

Authors: *S. DESAI, F. HAYDEN, M. WIGGINS, A. ETINGOF, Y. YANG, W. XU; Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Schizophrenia risk genes *Ngrn* (neurogranin, Ng) and *Grin2a* (GluN2A) encode proteins that regulate Ca^{2+}/calmodulin-dependent signaling and NMDA receptor function at excitatory synapses. During the visual critical period, Ng sequesters calmodulin to gate CaMKII and PP2B activity, while GluN2A-containing NMDARs shape the temporal profile of synaptic Ca^{2+} influx. We examined whether partial or complete loss of Ng and GluN2A, alone and in combination, disrupts dendritic spine density and binocular depth perception in layer II/III principal neurons of the primary visual cortex binocular area (V1B) using *Ngrn* and *Grin2a* knockout and heterozygous mice. Both male and female mice were used; no sex differences were detected and data were pooled by genotype. Complete Ng loss significantly reduced spine density compared to wildtype controls, while complete GluN2A loss did not. Combined haploinsufficiency of Ng and GluN2A produced a significant reduction in spine density not observed in either single heterozygous group; two-way ANOVA revealed a significant Ng genotype main effect ($p=0.025$), a non-significant GluN2A main effect ($p=0.530$), and a non-significant interaction ($p=0.922$), indicating the double heterozygous deficit reflects the near-significant Ng haploinsufficiency effect compounded by a small, individually undetectable GluN2A contribution, without evidence of epistatic interaction. Behaviorally, complete loss of either Ng or GluN2A significantly impaired shallow-side preference in a modified visual cliff paradigm (Ng KO $p=0.003$; GluN2A KO $p=0.019$), indicating disrupted depth perception. Ng heterozygosity alone was sufficient to impair depth perception ($p=0.006$), while GluN2A

heterozygosity produced a non-significant trend. Double heterozygotes showed significant behavioral impairment relative to wildtype (p=0.005). These results establish Ng as the primary determinant of excitatory synaptic maintenance and binocular circuit function, with GluN2A as a subordinate but consequential contributor when Ng-dependent signaling is partially compromised.

Disclosures: S. Desai: None. **F. Hayden:** None. **M. Wiggins:** None. **A. Etingof:** None. **Y. Yang:** None. **W. Xu:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.07/H4

Topic: A.10. Schizophrenia

Support: NIMH R21MH125012
NIMH MH096985

Title: Presynaptic molecular substrates of striatal dopamine signaling in schizophrenia

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Abstract: Widely replicated in vivo human imaging studies show that schizophrenia (SZ) is associated with elevated presynaptic dopamine (DA) synthesis and release in the striatum. This elevation is more pronounced in the associative striatum (AST), which includes the rostral caudate and putamen, than in the limbic striatum (LST), which includes the nucleus accumbens. DA synthesis, packaging into synaptic vesicles, and reuptake into the axonal bouton after release are governed by tyrosine hydroxylase (TH), vesicular monoamine transporter 2 (VMAT2), and dopamine transporter (DAT), respectively. To investigate whether altered levels of these proteins could contribute to elevated DA synthesis and release in the AST, we used multi-channel, fluorescence confocal microscopy to quantify TH, VMAT2, and DAT in the AST and LST of postmortem human SZ subjects. We hypothesized that elevated TH levels may underlie greater DA synthesis in SZ, accompanied by secondary increases in VMAT2 and lower DAT.
Postmortem human brain tissue was obtained from 27 pairs of age- and sex-matched SZ and unaffected comparison (UC) subjects (N=54). For each subject, a striatal section was labeled via immunohistochemistry for TH, VMAT2, and DAT. Single-plane images were collected at 20X and 0.325 μm^2 resolution using a spinning disk confocal light microscope. Micrographs were processed to exclude background signal, lipofuscin autofluorescence, and white matter. Mean fluorescence intensity of TH, VMAT2, and DAT was calculated in the AST and LST. Group differences in mean intensities were assessed using ANOVA.
Mean TH intensity was significantly (all $p<0.009$) 27.0% lower in the AST and 22.2% lower in the LST of SZ relative to UC subjects. Mean VMAT2 intensity was significantly 13.1% lower in

the AST ($p = 0.019$) and non-significantly 3.2% lower in the LST ($p = 0.704$) of SZ relative to UC subjects. Mean DAT intensity was non-significantly (all $p>0.05$) 13.3% lower in the AST and 18.5% lower in the LST of SZ relative to UC subjects.
Lower TH levels in the AST and LST suggest less DA synthesis, and lower VMAT2 levels in the AST suggest less vesicular packaging of DA. These findings contrast with evidence of elevated presynaptic DA synthesis and release in SZ in vivo. However, SZ subjects in this cohort were chronically treated with antipsychotic drugs (APDs), so the observed reductions may reflect treatment-related effects. APDs alleviate psychosis via blockade of postsynaptic D2 receptors, downstream of presynaptic DA measures. Thus, ongoing studies are investigating whether these findings reflect a secondary therapeutic mechanism of chronic APD treatment that may reduce presynaptic DA synthesis and packaging.

Disclosures: E.C. Russell: None. **K.N. Fish:** None. **J.R. Glausier:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.08/H5

Topic: A.10. Schizophrenia

Support: Stanley Family Foundation

Title: Tracking the evolving Brain-Wide Functional Connectome in psychiatric risk mouse models

Authors: *N. WANG[1], S. CHOI[1], X. LIU[2], Q. LIU[1], C. WU[1], S. LEE[1], X. YU[2], Z. FU[1];
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Abstract: Psychiatric disorders, including schizophrenia and bipolar disorder, are increasingly understood as disorders of distributed brain networks, characterized by highly complex symptoms that evolve dynamically over time. Although large-scale exome sequencing initiatives (SCHEMA/BipEx) have identified rare, high-risk loss-of-function variants, how these genetic liabilities disrupt brain-wide network trajectories remains unknown. Given the progressive nature of these disorders, systematically mapping network architecture across development is crucial for uncovering how early circuit abnormalities mature into manifest pathophysiology. To address this, we established a whole-brain functional connectivity framework using functional ultrasound imaging (fUS) for high-throughput, longitudinal resting-state connectomics across 10 SCHEMA/BipEx mutant mouse lines from Stanley Center.We acquired longitudinal resting-state fUS datasets from each line at 1, 2, and 3 months of age. The resulting dataset enabled 16 distinct genotype comparisons, including sex-stratified analyses. Region of Interest (ROI)-to-ROI Pearson correlation matrices were constructed to quantify genotype-dependent differences in functional connectivity. Across models, alterations in resting-state functional connectivity were developmentally dynamic and gene-dependent: some lines showed little divergence at 1

month but pronounced network reorganization by 2-3 months, whereas other lines manifested earlier aberrations and distinct, sex-dependent reversals in connectivity trends across age groups. Overall connectivity disruption progressively increased across development, peaking at 3 months. Despite the marked regional heterogeneity in susceptibility, vulnerable regions shared a non-linear longitudinal trajectory, characterized by the most significant alterations at 1 and 3 months, interspersed with a transient attenuation at 2 months. Specifically, the amygdala emerged as a prominent hub at 2 months, whereas the hippocampus showed the strongest convergence of network deficits by 3 months. Notably, the parietal cortex displayed sustained involvement across all developmental stages, while sensory cortical and amygdala engagement intensified later, indicating progressive recruitment of sensory-association and limbic circuitry.Together, these findings establish longitudinal fUS-based functional connectomics as a sensitive and scalable platform for mapping the systems-level trajectories of psychiatric risk genes and for screening candidate therapeutics designed to restore network balance.

Disclosures: N. Wang: None. **S. Choi:** None. **X. Liu:** None. **Q. Liu:** None. **C. Wu:** None. **S. Lee:** None. **X. Yu:** None. **Z. Fu:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.09/H6

Topic: A.10. Schizophrenia

Support: Stanley Family Foundation

Title: Multi-Scale Evidence for Hippocampal Dysfunction Following Nr3c2 Deficiency Identifies Neuropsychiatric Disease-Relevant Circuits

Authors: *R. LIN, T. YAU, A. ASAN, J. Q. PAN, S. SIMMONS;
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Abstract: The mineralocorticoid receptor gene NR3C2 has emerged as a candidate risk gene for neurodevelopmental as well neuropsychiatric disorders, including schizophrenia (SCZ) and autism spectrum disorder (ASD), yet the neural mechanisms through which NR3C2 contributes to disease-relevant phenotypes remain poorly understood. We combined behavioral, functional, transcriptomic, and single-cell approaches to define the consequences of Nr3c2 deficiency across multiple levels of brain organization.To determine how SCZ-associated NR3C2 loss-of-function contributes to brain dysfunction, we generated a mouse model carrying the SCZ case-derived premature termination variant Nr3c2(S306X). Nr3c2(S306X/+) mice exhibited impairments in spatial memory, social behavior, social memory, and sensorimotor gating. Transcriptomic profiling across multiple brain regions identified the hippocampus as the most vulnerable region, with enrichment of synaptic, membrane potential, cell adhesion, and GABAergic signaling pathways, including coordinated dysregulation of multiple GABA-A receptor subunits.Whole-

brain cFOS mapping revealed reorganization of hippocampal-centered activity networks, suggesting altered circuit-level coordination between hippocampal subregions and distributed brain regions. Single-nucleus RNA sequencing identified glutamatergic neurons as the primary cellular substrates of vulnerability. CA1, CA3, and dentate gyrus neurons exhibited highly concordant transcriptional responses enriched for synaptic and neuronal communication pathways. Regulon analysis further demonstrated coordinated remodeling of transcriptional regulatory programs across these neuronal populations, indicating a shared molecular response to Nr3c2 deficiency.Together, these findings identify the hippocampus as a convergent site of vulnerability to Nr3c2 deficiency across behavioral, circuit, cellular, and regulatory scales. Our results implicate Nr3c2 as a critical regulator of hippocampal network homeostasis and highlight mechanisms linking stress-responsive transcriptional programs to cognitive and social dysfunction relevant to schizophrenia and autism.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.10/H7

Topic: A.10. Schizophrenia

Support: CIHR Project Grant 190246

Title: Juvenile ventral hippocampal parvalbumin interneuron ablation produces schizophrenia-like behavioral deficits and disrupts hippocampal-prefrontal network dynamics in adulthood

Authors: J. C. ROBINSON[1], S. BHARDWAJ[2], M. P. BRANDON[1], *L. K. SRIVASTAVA[3]; [1]Psychiatry, McGill Univ., Montreal, QC, Canada; [2]Psychiatry, [3]Douglas Hosp. Res. Ctr., Montreal, QC, Canada

Abstract: Schizophrenia spectrum disorders (SSD) constitute a broad spectrum of disorders characterized by the presence of positive symptoms, negative symptoms, and cognitive impairments. While symptoms typically emerge in early adulthood, the neurodevelopmental hypothesis posits that circuit dysconnectivity begins in pre/perinatal or adolescence periods. Longitudinal studies implicate the ventral hippocampus (vHPC) as a primary locus of vulnerability, characterized by altered excitation-inhibition balance, and disrupted functional connectivity with the prefrontal cortex (PFC). These hippocampal abnormalities are closely linked to impairments in cognition, particularly working memory. Despite this, the specific cell populations and developmental mechanisms through which hippocampal dysfunction reshapes long-range network communication remain poorly defined. Parvalbumin-positive (PV+) interneurons are fast-spiking inhibitory neurons that regulate circuit excitability and network oscillations. Here, we test the hypothesis that selective disruption of PV+ interneurons in the

vHPC during development leads to persistent alterations in vHPC-PFC network synchrony that underlie cognitive deficits. We used transgenic PV-Cre mice and adeno-associated virus-mediated delivery of diphtheria toxin A to selectively ablate PV+ neurons in the vHPC during periadolescent development. In adulthood, mice were assessed using a battery of behavioral tasks including the Morris water maze, reversal learning, elevated plus maze, Y-maze, social novelty preference, and amphetamine-induced locomotion. A subset of animals was implanted with electrodes in the vHPC and medial prefrontal cortex (mPFC) for local field potential recordings during behavior. Our results show that juvenile vHPC PV interneuron ablation resulted in broad behavioral impairments, including deficits in reversal learning, impaired working memory, reduced social novelty preference, and enhanced sensitivity to amphetamine. Electrophysiological recordings revealed marked reductions in theta- and gamma-band power within both the vHPC and mPFC. In addition, ablated animals exhibit reduced vHPC-mPFC coherence, indicating disrupted communication across this circuit. These findings demonstrate that loss of vHPC PV interneurons during early development is sufficient to induce enduring behavioral and network abnormalities that resemble key features of schizophrenia. The results support a critical role for developmental hippocampal interneuron dysfunction in the emergence of hippocampal-prefrontal circuit deficits associated with neurodevelopmental disorders.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.11/H8

Topic: A.10. Schizophrenia

Support: P50MH136297

Title: Astrocytic IL6-CCL2 signaling in dorsal hippocampus drives ventral hippocampal dysfunction leading to psychosis-relevant behavior

Authors: *M. SINGH[1], I. MIURA[1], C. TRIPPAERS[1,2], B. J. LEE[1], B. BRONE[2], K. ISHIZUKA[1], A. SAWA[1,3,4];
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Abstract: A scientific approach in precision medicine is to start with observations in patients, followed by the synthesis and validation of a mechanism by using a cross-species approach or a back translation. In the present study, we uncover a novel mechanism mediated by an understudied, intra-hippocampal circuit, which is elicited by the coordinated activation of

interleukin-6 (IL6) and C-C motif chemokine ligand 2 (CCL2), driving psychosis-relevant behavioral changes.
We started from a comprehensive molecular assessment of the cerebrospinal fluid from the Johns Hopkins psychosis cohorts (69 patients, 55 controls) and identified IL6 and CCL2 as the molecules exhibiting the most robust changes that were positively correlated with each other. To address the mechanisms of the IL6-CCL2 interplay and resultant behavioral changes, we conducted literature mining to look for good models for investigating IL6 and CCL2, selecting cuprizone short-term exposure (CSE) and maternal immune activation (MIA) models.
The CSE model reportedly displays an upregulation of IL6 and CCL2 in the hippocampus, and in the present study we observed the upregulation of both molecules in astrocytes, selectively in the dorsal hippocampus (dHP), but not ventral hippocampus (vHP). Through cell type-specific molecular interventions, we showed that astrocytic IL-6 elevated astrocytic CCL2, which in turn activated the excitatory neurons throughout the dHP and resulted in amphetamine (AMPH)-induced hypersensitivity, a phenotype relevant to psychosis.
A major remaining enigma was why the activation of dHP excitatory neurons leads to the hypersensitivity driven by vHP excitatory neurons. We hypothesized that a specific intra-hippocampal mechanism relays the dHP activation to the vHP. After confirming the dCA3-vCA1 projection, we conducted a functional interrogation: optogenetic activation of the lateral dHP neurons induced vHP neuronal activation, whereas chemogenetic suppression of the dCA3-vCA1 projection rescued AMPH-hypersensitivity in the CSE mice. By using CA region-specific mice, we confirmed that the impact on the behavioral change was not mediated by dCA2 neuronal projections. These observations are being replicated in the MIA model. Together, we show a pivotal role for the dCA3-vCA1 projection in psychosis-relevant AMPH-hypersensitivity, in contrast to the dCA2-vCA1 projection for the social memory paradigm. Importantly, we demonstrated that the vCA1 neuronal sub-populations activated by AMPH were distinct from those involved in social memory. Here we show a functional segregation of vCA1 neuronal ensembles based on their dHP inputs, leading to distinct behaviors.

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Poster

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Program #/Poster #: PSTR298.12/I1

Topic: A.10. Schizophrenia

Title: Chronic haloperidol-induced dopamine supersensitivity in Disc1 mutant mice

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Abstract: Dopamine supersensitivity is a known consequence of prolonged antipsychotic treatment and is associated with adverse effects such as treatment resistance in schizophrenia. However, the mechanisms underlying this phenomenon remain unclear. In this study, we used heterozygous *Disrupted-in-Schizophrenia 1* (*Disc1* Het) mutant mice, a genetic model relevant to schizophrenia, to examine the development and neural correlates of dopamine supersensitivity following chronic haloperidol (HAL) exposure. Wild-type (WT) and *Disc1* Het mice of both sexes received an amphetamine (Amph; 2.5 mg/kg, i.p.) challenge to assess locomotor activity as a behavioral readout of dopamine reactivity. At baseline, Amph significantly increased locomotion in both genotypes, with Het mice showing a heightened response. To examine HAL-induced dopamine supersensitivity, mice were administered with HAL (0.5 mg/kg/day, i.p.) for 1, 2, 3, or 6 weeks, followed by an Amph challenge after a 3-day washout period. Chronic HAL treatment enhanced Amph-induced hyperlocomotion, indicative of dopamine supersensitivity, with onset occurring after 1 week in WT males, 2 weeks in WT females and Het males, and 3 weeks in Het females. Pretreatment with the dopamine D2 receptor (D2R) antagonist sulpiride reduced Amph-induced locomotor responses in HAL-treated mice, supporting the involvement of D2R-mediated mechanisms. However, chronic HAL treatment altered striatal D2R expression mainly in males, with increased D2R expression in WT males but not in Het males, while D1R expression remained largely unchanged and no significant receptor changes were observed in females. Morphological analyses revealed baseline reductions in dendritic complexity of medium spiny neurons (MSNs) in Het mice, while chronic HAL treatment reduced dendritic complexity in males and WT females but increased dendritic branching in Het females. Together, these findings suggest that chronic antipsychotic-induced dopamine supersensitivity involves both dopaminergic and structural adaptations in the striatum, and these changes are influenced by biological sex and *Disc1* mutation. This model offers a valuable tool for investigating the interaction between genetic vulnerability and chronic antipsychotic exposure in the emergence of dopamine supersensitivity, with implications for developing more personalized treatment strategies in schizophrenia.

Disclosures: C. Wu: None. **L. Lee:** None.

Poster

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Topic: A.10. Schizophrenia

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Title: Brain region-specific glutamatergic and bioenergetic dysregulations in macaque monkeys with DISC1 locus impairment

Authors: *Z. LAN[1,2,5], H. ONOE[3,6], T. TSUKIYAMA[7,5], N. OISHI[4], S.-I. URAYAMA[4], T. H. DINH[4], K. MIURA[5], A. SAWA[1,8], T. ISA[2,5,4,9];
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Abstract: Neurodevelopmental deficits frequently lead to adolescent social and cognitive changes that precede adult-onset psychiatric disorders. Although rodent models are widely used to address the mechanisms, their brains lack critical structures for human higher brain functions, such as the dorsolateral prefrontal cortex (DLPFC). To bridge this translational gap, we generated cynomolgus monkeys with *DISC1* locus impairment (DISC1-LI), targeting the multifunctional protein essential for neurodevelopment and involved in transdiagnostic mental health risks. Resting-state fMRI in this cohort revealed disrupted prefrontal functional connectivity and a shift in brain hub dominance from prefrontal to sensory areas, at ages equivalent to human adolescence. As clinical studies implicate diverse neurochemical alterations in psychiatric disorders, we extended this characterization to the neurochemical level using in vivo proton magnetic resonance spectroscopy (MRS) at 7-Tesla. DISC1-LI (n=5) and wild-type (WT, n=4) monkeys were examined at two developmental stages. At 3 years of age, voxels were placed in bilateral DLPFC (left/right DLPFC) and anterior cingulate cortex (ACC). At 4 years of age, voxels were placed in the ACC and bilateral thalamus (left/right thalamus). Metabolite concentrations were quantified using LCModel, correction for cerebrospinal-fluid partial volume, and included in analysis only when the Cramér-Rao lower bound was below 20%. At 3 years of age, combined glutamate and glutamine (Glu+Gln) was significantly reduced in the right DLPFC of DISC1-LI monkeys, whereas left DLPFC and ACC showed no group differences. At 4 years of age, phosphocreatine (PCr) was notably elevated in the ACC of DISC1-LI monkeys, while creatine (Cr) and other quantified metabolites were comparable between groups. These findings revealed region-specific, age-dependent neurometabolic alterations in DISC1-LI monkeys. The Glu+Gln reduction in the right DLPFC suggests compromised glutamatergic function that could be related to prefrontal connectivity alterations observed in this cohort. The selective PCr elevation with stable Cr indicates altered high-energy phosphate handling, mechanistically consistent with the role of DISC1 in mitochondrial function. Together, these sequential neurochemical changes may underlie the prefrontal network disruptions during adolescence and further support DISC1-LI monkeys as a translational platform for dissecting prodromal-stage neuropsychiatric pathophysiology and developmental trajectories relevant to schizophrenia.

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Poster

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Topic: A.10. Schizophrenia

Support: NIH MH107730
NIH P50MH136297

Title: Batten disease-like lysosomal deficits in a subset of patients with schizophrenia: an approach of precision psychiatry

Authors: *K. ISHIZUKA, A. HAYASHIDA, A. SAWA;
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Abstract: A scientific approach in precision medicine is to start with observations in patients, followed by the synthesis and validation of a working mechanism by employing a cross-species back-translation approach. In the present study, we discovered lysosomal deficits in a subset of schizophrenia (SZ) patients whose cellular signatures resemble Batten disease, a lysosomal storage disorder. Through the study of molecular and cellular alterations in biospecimens from SZ patients, we came across a significant increase in the level of cellular autofluorescence (AF). The increase in AF has been well known as a marker for lysosomal deficits and Batten disease. We hypothesized that at least a subset of patients with SZ might have lysosomal pathology, possibly associated with redox and autophagic cascade abnormalities. To address this question, we measured levels of 7 markers for lysosomal deficits in blood cells from 74 healthy controls (HC) as well as 71 SZ and 3 Batten disease patients. These include AF, globotriaosylceramide (Gb3), ATP synthase subunit c (SubC), cathepsin B, lysosomal-associated membrane protein 1 (LAMP1), p62/sequestosome-1, and microtubule-associated protein 1A/1B-light chain 3 (LC3-II/I). Among the markers, a significant increase in AF and Gb3 was observed in SZ and Batten disease patients compared with the HC group. When we employed a composite score for both AF and Gb3, we observed a robust difference between Batten disease patients and HCs with no overlap at the individual subject level. We also observed a significant difference between SZ patients and HC subjects. Twelve out of 71 SZ patients (17%) showed higher scores than any HC subject, indicating that Batten disease-like lysosome pathology may underlie this subset of SZ. Given that these abnormalities are frequently associated with the deficits of peroxisome proliferator-activated receptor gamma (PPARγ) pathway, we used a PPARγ agonist and observed its beneficial effects on the molecular changes. In addition, to address whether Batten disease animal models may also show behavioral changes relevant to psychiatric manifestations, we conducted a series of behavior tests. Significant deficits were observed in novel object recognition test, resident intruder test, fear conditioning test, and pentylenetetrazol seizure threshold test, whereas their motor functions were intact. We also preliminarily observed that the PPARγ agonist ameliorated the behavioral deficits. Under the lens of precision psychiatry, we have defined an understudied pathology underlying a subset of SZ patients. This is crucial for a conceptual breakthrough in academic psychiatry and translational drug discovery.

Disclosures: K. Ishizuka: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US20250144101A1. **A. Hayashida:** None. **A. Sawa:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; research grant from Sumitomo Pharma, research grant from Sysmex. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US20250144101A1.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.15/I4

Topic: A.10. Schizophrenia

Support: Intramural Grant in aid

Title: VIPR2 Copy Number Variation Drives Th2-Mediated Cardiac Remodelingand Dilated Cardiomyopathy in a Mouse Model of Schizophrenia

Authors: X. TIAN[1], B. HAN[2], *J. LI[3], X. ZHANG[4], F. HUANG[5], X.-H. LU[6];
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Abstract: Vasoactive intestinal peptide receptor 2 (VIPR2) copy number variation (CNV) is among the strongest recurrent genetic risk factors for schizophrenia (SCZ), yet its effects beyond the central nervous system remain largely unexplored. Because patients with SCZ exhibit increased cardiovascular morbidity, including dilated cardiomyopathy (DCM), we investigated whether VIPR2 overexpression contributes to cardiac pathology. Using a VIPR2-CNV mouse model, we previously showed that VIPR2 overexpression induces social deficits, Th2-skewed immune activation, and elevated IL-4 production. Here, we tested the hypothesis that VIPR2 overactivation induces an early and sustained Th2-biased immune response that drives progressive cardiac remodeling and dilated cardiomyopathy (DCM). Cardiac function was assessed by transthoracic echocardiography in aged VIPR2-CNV mice and wild-type littermates. Histological and molecular analyses were performed to evaluate cardiac remodeling, fibrosis, and inflammatory responses. Immune phenotypes were characterized by using flow cytometry and cytokine analyses. VIPR2-CNV mice developed progressive cardiac dysfunction, including significantly reduced ejection fraction (21%) and fractional shortening (27%), increased left

ventricular dilation, and impaired systolic function, consistent with dilated cardiomyopathy. Molecular analyses revealed significant upregulation of fibrosis-associated markers, including α-smooth muscle actin (α-SMA) and periostin, indicating active fibrotic remodeling. Enhanced Th2 polarization and elevated IL-4 production were observed in VIPR2-CNV mice, implicating IL-4 as a potential mediator linking immune dysregulation to cardiac pathology. Consistent with this hypothesis, Mendelian randomization analysis of human genetic datasets identified IL-4 as a putative causal factor associated with DCM risk. Together, these findings identify a previously unrecognized neuroimmune mechanism linking a schizophrenia-associated genetic risk factor to progressive cardiac dysfunction. Our results support a model in which VIPR2 overexpression drives chronic Th2-biased immune activation, resulting in sustained IL-4 signaling, cardiac remodeling, fibrosis, and the development of dilated cardiomyopathy. By establishing a mechanistic connection between schizophrenia-associated genetic variation and cardiac disease, this study identifies Th2 cytokine signaling as a promising therapeutic target and suggests a potential strategy for preventing cardiovascular complications in patients with schizophrenia.

Disclosures: X. Tian: None. **B. Han:** None. **J. Li:** None. **X. Zhang:** None. **F. Huang:** None. **X. Lu:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.16/I5

Topic: A.10. Schizophrenia

Support: Intramural research support NIMH

Title: N-terminal-binding PAGE5-IgG autoantibodies in a subset of early-onset psychosis

Authors: *R. TYAGI[1], J. YANG[2], C. BLUCHER[3], D. MATHALON[4], P. KHIL[5], T. ESPARZA[1], A. BESTERMAN[6], C. M. BARTLEY[7];
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Abstract: Background: It has been hypothesized that autoimmunity plays a role in a subset of cases with early-onset psychosis (EOP), but clinically diagnostic autoantibodies are uncommon in EOP patients without neurologic features. **Methods:** EOP cases with first episode psychosis (N=30, ages 11-17 years) were consecutively enrolled at UCSD. Demographically similar healthy subjects (N=30, ages 13-24 years) and recent-onset schizophrenia (ROS; N=36, ages 12-36 years), enrolled in a UCSF psychosis study, and NIH blood bank healthy adult donors (N=31) were selected as comparators. All studies were IRB-approved. Sera from each cohort was screened by full-length human proteome microarray (HuProt™ v4.0). Candidate autoantibodies

were validated by direct immunoblotting, and enzyme-linked immunosorbent assay (ELISA). To investigate the immunodominant epitope, truncated N- and C-terminal P-antigen family protein (PAGE)-5 fragments were expressed in E. coli. N- and C-reactive PAGE5 antibodies were isolated from a commercial polyclonal anti-PAGE5 using cyanogen bromide immunoaffinity purification. The specificity and cross-reactivities of N- and C-terminal PAGE5 antibodies were assessed by ELISA and protein microarray, respectively. One-sided Fisher's exact test was used to test for significant differences in PAGE5-IgG frequencies among cohorts. **Results:** Known autoimmune encephalitis antibodies were not detected in EOP. PAGE5 was identified as a candidate autoantigen by protein array in 3/30 EOP cases and validated by immunoblot. Subsequent ELISA revealed that PAGE5-IgG was significantly more frequent in EOP (4/30; OR-9.23; p=0.05) and nominally more frequent in clinically high risk (2/39; OR-3.24; p=0.34) and ROS (3/27; OR-7.50; p=0.087), compared to pooled healthy control (1/61)—suggesting that PAGE5-IgG is more prevalent in EOP. In aggregate, PAGE5-IgG was significantly more frequent in psychotic spectrum cases (N=9/96) than controls (N=1/61) (OR = 6.3, P=0.046). We measured N- and C-terminal PAGE5-IgG (N-PAGE5 and C-PAGE5, respectively) in our cohorts by ELISA. Likewise, we found that EOP and ROS cases were more likely to exhibit an N-terminal bias, with an N/C ratio greater than 1.5 found exclusively among individuals in the psychotic spectrum. Because PAGE5 is not expressed in brain, we developed an assay to isolate N- and C-terminal reactive PAGE-IgG and validated using commercial polyclonal antibodies followed by ELISA and protein microarray. **Conclusion:** PAGE5-IgG is more frequent in EOP than in controls and preferentially binds to N-terminal epitopes. The pathogenic relevance of PAGE5-IgG is unknown, but may involve molecular mimicry.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.17/I6

Topic: A.10. Schizophrenia

Title: Molecular adaptations of activated T-cells in an inflammation-associated schizophrenia subgroup

Authors: *R. K. O'HARA-PAYNE[1], D. SALEM[3], S. M. CLARK[2], M. E. CORTES-GUTIERREZ[4], N. SINGH[5], D. L. KELLY[6], S. A. AMENT[7];
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Abstract: Schizophrenia is a debilitating psychiatric condition affecting about 3.7 million people in the United States. Approximately 35% of those with schizophrenia-related disorders (SRD) have a gluten intolerance characterized by an immune response to gliadin, a component of gluten. This anti-gliadin antibody-positive(AGA IgG+) subgroup also exhibits increased negative symptoms and inflammation in the peripheral blood and brain. Historically, negative symptoms have been more difficult to treat than positive symptoms, but in this subgroup, negative symptoms have been shown to improve with a gluten-free diet. To better define the immune mechanisms contributing to differences in symptomatology, we characterized transcriptional signatures of peripheral immune cells in AGA+ SRD (n=7) compared to AGA-negative (AGA-) SRD (n=3)and healthy controls (HC; n=5), using single-cell RNA-sequencing (scRNA-seq)of peripheral blood mononuclear cells (PBMCs; n=61,001). AGA+ SRD was associated with increased abundance of T-helper-17 cells (Th17), T-follicular helper-1 (Tfh1), CD5+ B cells, plasmacytoid dendritic cells (pDCs), and severalCD8+ T cell subsets, including memory and Natural Killer-T-like activated subsets. In parallel, AGA- SRD exhibited a higher abundance of several monocyte subsets compared to either AGA+ SRD or HC. Pathway analysis revealed upregulation in AGA+ SRD of JAK/STAT, type I Interferon, and IL-6signaling pathways in distinct subsets of activated T cells. Collectively, these
results define a unique T-cell-predominant inflammatory signature in AGA+ SRD, as well as potential targets for therapeutic intervention.

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Poster

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Topic: A.10. Schizophrenia

Support: NIMH Grant NCT00001486, Annual report no. ZIA MH002942053

Title: Investigating the impact of common genetic risk variants for schizophrenia on neuronal function and elucidating relationships between cellular phenotypes, clinical status and cognitive performance

Authors: *D. DAS[1], G. SHIM[2], F. FARINELLI[3], S. SRIPATHY RAO[4], I. OSTLUND[5], R. E. STRAUB[4], B. J. MAHER[6];
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Abstract: Schizophrenia (SCZ) is a highly polygenic disorder characterized by substantial clinical variability and a lack of well-defined cellular or pathological mechanisms. Advances in human induced pluripotent stem cell (hiPSC) technology have enabled the modeling of SCZ-associated polygenic risk and identified cellular phenotypes linked to SCZ diagnosis, but their relevance to the disorder's clinical manifestations and cognitive impairments remains uncertain. In this study, we examined how cellular characteristics observed in hiPSC-derived neurons relate to an individual's diagnostic status, symptom severity, and cognitive function. As part of our discovery study (Page et al, PNAS 2022) we reprogrammed, differentiated and characterized neuronal populations and cellular activity of iPSC lines from 13 high PRS individuals with schizophrenia (SCZ) and 15 low PRS neurotypical individuals (CON). We performed RNAseq, whole-cell electrophysiology, and high-content imaging. All experiments and data collection were done blind to diagnosis and clinical and cognitive phenotypes. We found alterations in electrophysiological properties of voltage-gated sodium channels (VGSCs) in SCZ neurons compared to CON. SCZ neurons showed increased membrane resistance, increased number of sodium current peaks in response to a voltage ramp protocol, a hyperpolarized shift in VGSC activation and inactivation and reduced long-term inactivation indicating altered neuronal excitability driven by altered VGSC channel kinetics. SCZ neurons also showed increased frequency of spontaneous inhibitory postsynaptic currents (siPSC) but no difference in the frequency of spontaneous excitatory postsynaptic currents (sEPSC), suggesting an excitatory-inhibitory imbalance. Interestingly, some electrophysiological measures correlated with the individual's clinical symptoms and cognitive performance whereby increased number of VGSC peaks were associated with the severity of hallucinations and delusions whereas sEPSC amplitudes correlated with negative symptoms and cognitive impairment. We subsequently performed an initial replication study of independent genomes: 8 high PRS SCZ and 3 low PRS CON and showed recapitulation of the VGSC phenotypes and association between cellular measures and the donor's diagnosis and/or clinical/ cognitive phenotypes. Integration of analyses from our diverse data sets will help identify pathological cellular and molecular pathways and biomarkers for possible therapeutic intervention.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Program #/Poster #: PSTR298.19/I8

Topic: A.10. Schizophrenia

Support: NIMH-IRP ZIC MH002903

Title: Single nucleus transcriptomics reveals neurodevelopmental, synaptic, and metabolic dysfunction in excitatory neurons and glia of the prefrontal cortex in schizophrenia

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Abstract: Prior studies have implicated cell type-specific gene expression changes in excitatory neurons of the prefrontal cortex in the pathogenesis of schizophrenia (SCZ), and functional enrichment analyses have implicated neurodevelopmental and synaptic processes. Mounting evidence also supports a role for non-neuronal cells, particularly astrocytes, in the dysregulation of genes involved in synaptic functions in SCZ. To further characterize the cell type-specific genomic mechanisms underlying SCZ, we performed single nucleus RNA sequencing on the dorsolateral prefrontal cortex (dlPFC) of 23 cases with SCZ (7F, mean age = 55.1$\pm$12.3) and 21 controls (7F, mean age = 50.8$\pm$14.5). Our final dataset captured 393,000 nuclei across 16 excitatory, 19 inhibitory, and 11 non-neuronal cell classes. We conducted differential gene expression (DE) analysis and gene set enrichment analysis (GSEA) controlling for sex, race, post-mortem interval, RNA integrity number, %mitochondrial RNA, %ribosomal RNA, and cellular detection rate. DE analysis revealed transcriptional dysregulation in >2,500 genes (padj < 0.05; |logFC| > 0.231) across 44 cell types, primarily in superficial (n=1,028, 3 subtypes) and deep layer (n=441, 4 subtypes) excitatory neurons, astrocytes (n=446, 2 subtypes), and oligodendrocytes/OPCs (n=368, 2 cell types). Inhibitory neurons showed minimal differential expression, apart from one class of parvalbumin-expressing interneurons (n=227). GSEA identified downregulation of genes involved in development, cell differentiation, lipid metabolism, and synaptic signaling in excitatory neurons, and upregulation of these same pathways in glial cell types. Integration with a developmental transcriptomic dataset revealed that genes upregulated in excitatory and glial cells in SCZ are preferentially expressed in the third trimester and adulthood, whereas downregulated genes are preferentially expressed in early childhood and adolescence. Results suggest concerted involvement of excitatory neurons and glia in disruption of neurodevelopmental, synaptic and metabolic processes across specific developmental windows in SCZ. Our ongoing analysis is focused on investigating the regulatory mechanisms that underlie transcriptomic dysregulation in SCZ.

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Poster

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Title: Loss-Of-Function Perturbations Across over 100 Neurodevelopment and Psychiatric Disorders Risk Genes Reveal Convergent Molecular Signatures

Authors: *C. THAPA[1], H. ZHANG[1], S. DIAZ DE LEON-GUERRERO[3], E. OH[1], P. GOWDA[5], D. J. SIRKIN[1], A. BARISHMAN[1], M. ELACHWAH[6], A. MCCARROLL[1], L. PEYTON[2], S. ZHANG[7], R. POLLAK[8], R. P. HART[9], C. N. PATO[10], A. KREIMER[11], A. SANDERS[1], J. G. MULLE[12], Z. P. PANG[4], J. DUAN[13];
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Abstract: The mechanistical understanding of neurodevelopmental and psychiatric disorders (NPD) has been constrained by individual studies focusing on limited number of genes. Here, we conducted a large-scale, unbiased perturbation of about 200 NPD genes using induced pluripotent stem cell (iPSC)-derived neurons on different genetic backgrounds. In this study, loss-of-function (LoF) human iPSC lines were differentiated into excitatory and inhibitory neurons, co-cultured with mouse astrocytes, and subjected to single-cell RNA-sequencing (scRNA-seq) profiling. For the 107 genes, including 19 SCHEMA schizophrenia (SCZ) and 61 autism spectrum disorder (ASD) risk genes, we employed an efficient and scalable CRISPR DNA base editing pipeline to derive LoF lines from four independent iPSC lines of European ancestry (CW20107, KOLF2.2J, CD14, and CD19). After stringent scRNA-seq data quality control, we characterized 311,471 excitatory neurons and 226,145 inhibitory neurons. We performed differentially expressed gene (DEG) analysis by comparing each LoF perturbation to its corresponding control (NTC) within each neuronal subtype. To assess the transcriptional convergence among NPD categories, we conducted Jaccard similarity analyses based on the

overlap of significant DEGs. We also performed Spearman correlation analysis using log_2 fold changes of these genes. These analyses revealed distinct clustering patterns, across different LOF genes showing shared transcriptional responses. Gene set enrichment and clustering analyses of DEGs revealed convergent modules characterized by dysregulation of genes related to neuronal development and synapse assembly, which often accompanied by expression alteration of genes involved in lipid/cholesterol synthesis and mitochondrial function. Weighted Gene Co-expression Network Analysis (WGCNA) and LINGER (LIfelong neural Network for GEne Regulation) further identified co-expressed gene modules and gene regulatory networks (GRNs) that capture cell type-specific, disease convergent or divergent transcriptional changes across NPD perturbations. Both ASD- or SCZ-associated GRNs were found enriched for ASD risk genes (from Safari) and SCZ GWAS risk genes, suggesting a convergent gene regulatory program across disorders. Overall, our analyses of the of NPD LoF genes lay the ground for identifying convergent molecular signatures across NPD risk genes in the SSPsyGene project.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

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Program #/Poster #: PSTR298.21/J2

Topic: A.10. Schizophrenia

Support: R01MH136706
R01MH134893

Title: Schizophrenia in 22q11.2 deletion syndrome is associated with impaired neuronal mitophagy

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Abstract: Background and Objectives 22q11.2 deletion syndrome (22qDS) is a prevalent chromosomal microdeletion that confers a 25-fold increased risk for schizophrenia (SZ), a condition affecting approximately 1% of the global population. Despite this significant genetic risk, 75% of individuals with 22qDS do not develop psychosis, suggesting the existence of protective mechanisms that influence variable penetrance. While the most common 22qDS deletion impacts seven genes encoding mitochondria-localizing proteins, the precise contribution of mitochondrial deficits to SZ onset remains largely undefined. Building on prior findings where stem-cell derived neurons (iNeurons) from non-psychotic 22qDS (22qDS-SZ) individuals

upregulate mitochondrial biogenesis genes while those with SZ (22qDS+SZ) exhibit weaker energetics, this study investigates the underlying mechanisms of these energetic defects. MethodologyIn this case-control study, we utilized fluorescent markers and live-cell imaging assays to evaluate mitochondrial health, age, and turnover alongside lysosomal function in iNeurons. We analyzed parameters such as mitochondrial depolarization and lysosomal pH, as well as proteomics and transcriptomic approaches. The study compared 6 control lines (ages 22-30) to 5 22qDS-SZ lines (ages 22-37) and 5 22qDS+SZ lines (ages 18-27). 22qDS groups were grossly matched for age, sex, IQ, and comorbid psychiatric diagnoses.
Findings and ImplicationsOur analysis revealed that 22qDS+SZ iNeurons retained a distinct population of older, more depolarized mitochondria relative to controls and 22qDS-SZ groups. Transcriptomic and proteomic analysis revealed that 22qDS+SZ iNeurons had reduced expression of autophagy and mitophagy-related pathways and expressed genes linked to lysosomal storage diseases. The 22qDS+SZ group showed impaired lysosomal degradative capacity (mean±SD: 22q+Sz 11.2±2.54; 22q-Sz 17.69±3.41; controls 17.05±3.35) driven by elevated lysosomal pH that resulted in slowing of mitophagy. Restoring lysosomal acidification with acidifying nanoparticles rescued lysosomal function, improving mitophagy and mitochondrial turnover in 22qDS+Sz iNeurons. These findings identify reversible mitophagy defects as a novel therapeutic target for schizophrenia within the 22qDS population. Moreover, this study sets the groundwork for exploration in other mitochondria-heavy tissues linked to neurological disease, such as the blood-brain barrier.

Disclosures: A.F. Edwards-Cintrón: None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.23/J3

Topic: A.10. Schizophrenia

Title: Neurodevelopmental signatures of co-expression network abnormalities versus gene expression differences in schizophrenia

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Abstract: Background: Our work on gene co-expression networks from postmortem brain bulk RNA-seq identified differentially connected genes (DCG) in controls versus schizophrenia donors. Functional profiling and validation analyses of DCG, including neurodevelopmental trajectory analysis in human brain organoids, brought additional biological insight about schizophrenia etiopathogeny comparative with differentially expressed genes (DEG). Methods: Sets of DCG defined by network topology analysis (clustering coefficient C=286, intra-modular

connectivity kIn = 185, “C and kIn shared” = 242) and regional consistency across three brain regions (DLPFC, hippocampus and caudate), and sets of DEGs (DEG_{DLPFC}=68, $DEG_{hippocampus}$=76, $DEG_{caudate}$=1945) were examined. “Pseudotime” trajectories- surrogates of developmental stages- were calculated with *Monocle v.3* from four sets of human brain organoids: cerebral- COs, ventral striatal- VSO, hippocampal, and oligospheroids- hOL. Neurodevelopmental signatures (the significant overlap between DCG, DEGs and genesets with significant expression shifts by the developmental stage of cells ordered along trajectories) were functionally profiled by biological ontologies (GO:BP). Results: All sets of DCG showed significant reliable neurodevelopmental signatures (p_{adj}<0.05; odds ratio- OR ≥ 3) with the strongest effect for the overlap between “C and kIn shared” and genesets from hOL (OR = 11.9). The overlap between “C and kIn shared” and hOL genesets (n=103 genes) was uniquely associated with myelination and myelin assembly. Two sets of kIn neurodevelopmental signatures, (i.e., intersections with VSO genesets) shared the annotation of “modulation of chemical transmission”. In contrast, only $DEG_{caudate}$ showed weaker neurodevelopmental signatures (p_{adj}<0.05; odds ratio- OR < 3) enriched in biological ontologies related to forebrain development, axonogenesis, cytoplasmic translation and cilium movement. Conclusion: Our results suggest stronger neurodevelopmental signatures of co-expression network abnormalities compared with differential gene expression in schizophrenia.

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Poster

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Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.24/J4

Topic: A.10. Schizophrenia

Support: State assignment of the Federal State Budgetary Scientific Institution, “Petrovsky National Research Centre of Surgery” FURG-2025-0031

Title: DRD2 and corpora amylacea distribution in human olfactory bulb in patients with schizophrenia

Authors: *A. MALKOV[1,2], A. PROSHCHINA[1], Y. KRIVOVA[1], A. KHARLAMOVA[1], O. GODOVALOVA[1], V. GULIMOVA[1], S. SAVELIEV[1];
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Abstract: Schizophrenia is a severe psychiatric disorder with an incompletely understood pathogenesis. The dopaminergic hypothesis remains one of the leading models, linking clinical manifestations to altered dopamine signaling. Dopamine D2 receptors (DRD2) are highly expressed in the olfactory bulb (OB), the primary central structure for olfactory processing.

Several studies have demonstrated structural abnormalities of the OB in schizophrenia, including reduced bulb volume. In addition to its sensory function, the OB represents an important glymphatic outflow pathway. Glymphatic dysfunction has been implicated in schizophrenia by neuroimaging studies. Histological indicators of impaired glymphatic clearance in the OB include corpora amylacea (CA) accumulation and altered aquaporin-4 polarization.The present study aimed to compare DRD2 expression and CA density in the OB of patients with schizophrenia and unaffected controls and to evaluate potential associations between these parameters. Postmortem OB samples from patients with schizophrenia (n=10) and matched controls (n=10) were examined. Each bulb was serially coronal sectioned, and representative rostral, middle, and caudal sections were analyzed. Sections were stained using PAS histochemistry and IHC for DRD2. Whole-slide images were processed in QuPath using a trained artificial intelligence-based algorithm. The proportion of DRD2-positive area relative to total tissue area was quantified automatically. CA were identified using threshold-based segmentation, and their density was calculated per unit area. Group comparisons were performed using Student's t-test following assessment of normality and homogeneity of variance.No significant differences in DRD2+ area were detected between schizophrenia and control groups. CA density demonstrated a trend toward reduction in schizophrenia but did not reach statistical significance. A strong positive correlation between DRD2 expression and CA density was observed in controls ($r=0.70$, $p < 0.05$) but was absent in schizophrenia.These findings do not support altered DRD2 expression in the OB of patients with schizophrenia. However, the disruption of the normal relationship between DRD2 expression and CA density, together with the observed tendency toward reduced CA accumulation, may indicate altered glymphatic homeostasis in schizophrenia. Larger cohorts, stratification by age and sex, and spatially resolved analyses may further clarify these associations.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.25/J5

Topic: A.10. Schizophrenia

Title: Computational Phenotyping of Psychosis Risk: Microstate State and Transition Surprisal Unmasks Stress-Vulnerable Neural Dynamics Following the Trier Social Stress Test

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Abstract: Intro: Adolescent development is a critical period for the development of psychosis, particularly in youth at clinical high risk (CHR+). The integration of information theory and EEG microstates provides a novel framework for quantifying these dynamics. State surprisal quantifies the unexpectedness of an individual microstate occurrence relative to baseline, whereas transition surprisal quantifies the unpredictability of switching between microstates. Identifying stress-induced alterations in these measures may improve early detection and intervention strategies for youth at elevated risk of psychosis. Hypothesis: We hypothesized that CHR+ periadolescents would exhibit significantly elevated post-stress transition surprisal relative to controls. Methods: The study enrolled 167 periadolescents (12.6 ± 2.3 years; range 9-16; 61 female), including 42 CHR+ individuals and 125 controls (CHR-). Symptom severity was assessed using the Scale for the Assessment of Positive Symptoms and the Scale for the Assessment of Negative Symptoms. Acute stress was induced using the Trier Social Stress Test for Children. Resting-state EEG was acquired before and after stress induction. EEG data were segmented into four canonical microstates using a modified K-means clustering algorithm. State and transition surprisal features were extracted from the resulting symbolic sequences and compared across groups. Results: Post hoc analyses revealed substantially greater post-stress alterations in CHR+ youth than controls. The most significant changes in the CHR+ group included State Surprisal A ($p = .021$), State Surprisal C ($p < .001$), and all State C transition surprisal measures. In contrast, controls demonstrated more limited alterations, entropy rate ($p = .015$) and State C Surprisal ($p = .004$), without significant changes in State C transition surprisal. Direct group comparisons revealed significant differences between CHR+ and control participants in and State A and State C Surprisal (both $p < .03$). Conclusion: This novel information-theoretic analysis reveals significant alterations in cortical network dynamics among periadolescents at clinical high risk for psychosis prior to the onset of a first psychotic episode. Notably, alterations were observed in both transition and state surprisal measures, suggesting that psychosis risk is associated not only with changes in the temporal context in which microstates occur, but also with changes in the occurrence patterns of the microstates themselves. These findings support microstate surprisal as a promising biomarker of stress-related network dysfunction in youth at elevated risk for psychosis.

Disclosures: A. Blumsack: None. **A. Winn:** None. **J. Mark:** None. **A. Belger:** None.

Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.26/J6

Topic: A.10. Schizophrenia

Support: Wellcome Trust & IBRO:25NCAMH-3028803892

Title: Decoding the Non-Coding Genome in Schizophrenia: A T-UCR Expression Signature Enables High-Accuracy Blood-Based Diagnosis via Machine Learning

Authors: *F. HANIF[1], Q.-U.-A. AMIR[2], D. TABASSUM[3], R. KHAN[3], N. IQBAL[4], W. WASHDEV[3], R. ABOUNADER[5];
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Abstract: Background: Schizophrenia lacks reliable molecular biomarkers, and diagnosis remains symptom-based. Transcribed ultraconserved regions (T-UCRs), a subclass of long non-coding RNAs encoded by sequences completely conserved across human, mouse, and rat genomes, have established regulatory roles in cancer. Given the documented molecular overlap between schizophrenia and cancer including shared signaling pathways and susceptibility loci, we investigated whether breast cancer-associated T-UCRs are dysregulated in schizophrenia and could serve as peripheral blood biomarkers. Methods: Six candidate T-UCRs (uc.38, uc.51, uc.63, uc.84, uc.147, and uc.183), previously reported as dysregulated in breast cancer, were analyzed. A competing endogenous RNA network was constructed to identify target genes and pathways. Protein-protein interaction analysis and validation using the peripheral blood dataset GSE27383 were performed. Expression of candidate T-UCRs was quantified in whole blood samples from 100 schizophrenia patients and 100 healthy controls recruited in Karachi, Pakistan. Partial least squares discriminant analysis (PLS-DA) and machine learning approaches were used to evaluate diagnostic performance. Results: The six T-UCRs collectively regulated 507 genes enriched in dopaminergic and cholinergic signaling, axon guidance, and neurodevelopmental pathways. KRAS, CREB1, and RUNX1 emerged as central hub genes, while CD44, CDC42, and KRAS were consistently upregulated in the validation dataset. Five T-UCRs (uc.38, uc.51, uc.63, uc.84, and uc.183) were significantly differentially expressed between cases and controls ($p<0.05$). PLS-DA identified uc.63 and uc.84 as the strongest discriminators, with variable importance in projection scores exceeding 1.0. A three-transcript signature achieved an area under the curve of 0.854 using random forest classification with 10×3-fold cross-validation. T-UCR expression did not correlate with PANSS severity scores, suggesting a trait-dependent rather than state-dependent molecular signature. Conclusions: This study provides the first evidence of T-UCR dysregulation in schizophrenia and identifies a minimally invasive three-transcript blood-based signature with high diagnostic accuracy. These findings reveal a previously unexplored non-coding regulatory axis with potential applications in biomarker development and precision psychiatry.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.27/J7

Topic: A.10. Schizophrenia

Title: Mapping Protein Network Rewiring by Schizophrenia Risk Mutations

Authors: *R. VARTAK[1,3], N. SUN[4], B. WANG[5], E. MARTINEZ[4], J. DEA[1,4], R. SCHEIN[4], K. OBERNIER[2], M. STATE[5], N. J. KROGAN[3];
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Abstract: Determining whether protein-protein interaction (PPI) networks can uncover precise causal mechanisms driving human disease remains a major challenge. Having previously deployed a network-based framework to decode autism spectrum disorder (ASD) pathology, here, we expand this paradigm to schizophrenia (SCZ). We systematically mapped PPIs for 32 high-confidence SCZ risk genes in HEK293T cells, uncovering ~500 interactions—75% of which are previously unreported. These SCZ interactors are highly expressed in the human brain, show synaptic enrichment and converge on key pathways implicated in SCZ pathogenesis, including DNA repair, synaptic vesicle recycling, and proteasomal degradation. By leveraging AlphaFold and assessing the impact of over 50 pathogenic missense mutations across multiple SCZ genes, we mapped wild-type protein complexes alongside those that are selectively rewired by disease mutations; for example, specific *CUL1* patient mutations rewire interactions with key components of the ubiquitin-proteosome pathway. This work offers new insights into the molecular mechanisms driving SCZ pathology and establishes a powerful, scalable platform to develop and test therapeutic strategies for genetically defined conditions.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR298.28/J8

Topic: A.10. Schizophrenia

Support: Brain Science Convergence Research Program (RS-2023-00266120)
Basic Science Research Program (RS-2026-25470841)
Basic Research Program (25-BR-05-05) of the Korea Brain Research Institute (KBRI)
Basic Science Research Program (RS-2025-25419331

Title: Cortico-striato-thalamo-cerebellar dysconnectivity across the psychosis spectrum: a multicenter spectral DCM study

Authors: *M. HA[1,2,3], E. CHOE[2,4,5], M. KIM[2,4,3];
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Korea, Republic of; [4]Dept. of Neuropsychiatry, Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [5]Dept. of Clin. Pharmacol. and Therapeutics, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Cortico-striato-thalamic dysconnectivity has been considered one of the key circuit abnormalities in psychosis. Although cerebellar pathways are closely linked to this circuit, the direction and strength of these interactions remain unclear because most studies have relied on undirected functional connectivity. We examined effective connectivity among cortical, striatal, thalamic, and cerebellar regions across the psychosis spectrum using spectral dynamic causal modelling. Resting-state fMRI data were acquired across five sites in South Korea, including 458 healthy controls (HCs), 175 clinical high-risk individuals (CHR), 171 first-episode psychosis patients (FEP), and 234 schizophrenia patients (SCZ). A fully connected model was specified among 10 regions of interest: higher-order and sensory thalamus, associative and limbic striatum, cerebellar Crus I and II, anterior insula (AI), dorsolateral prefrontal cortex, ventromedial prefrontal cortex (vmPFC), and temporoparietal junction. Group differences were estimated using Parametric Empirical Bayes while controlling for age, sex, head motion, and site. Bidirectional hypoconnectivity among the thalamus, striatum, and cerebellum was present in CHR and became more extensive in FEP and SCZ. Effective connectivity from the thalamus and cerebellum to the AI was increased across all three clinical groups, with larger effects in later illness stages. FEP additionally showed bidirectional striato-thalamic hypoconnectivity and altered cerebellar-prefrontal connectivity. SCZ showed the most enhanced self-inhibition across thalamic, striatal, insular, and prefrontal regions and decreased vmPFC-to-limbic striatal connectivity. These findings suggest that cerebellar-subcortical dysconnectivity emerges in CHR and expands across FEP and SCZ, alongside increased thalamo-cerebellar influence on the AI and broader inhibitory alterations in SCZ.

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Poster

PSTR298: Schizophrenia Genetics, Pathophysiology, and Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR298.29/K1

Topic: A.10. Schizophrenia

Support: MH 111177

Title: Network heterogeneity in schizophrenia: Application of Transitive Maximal Correlation to task-driven fMRI data

Authors: A. ALAZO[1], J. HADOUS[2], H. ABDALLAH[2], J. A. STANLEY[3], A. SALCH[2], *V. A. DIWADKAR[4];
[1]Harvard Univ., Boston, MA; [3]Psych & Behav Neurosci, [2]Wayne State Univ., Detroit, MI; [4]Wayne State Univ. SOM, Detroit, MI

Abstract: Dysconnection in schizophrenia (SCZ) is typically investigated after functional imaging data are summarized (Silverstein et al., 2016) following which summaries are submitted to parametric or graph theoretic analyses (Meram et al., 2023). In healthy brains, task-driven activity drives functional sub-network segregation in the service of implementation efficiency. Moreover, these sub-networks may be organized around specific brain regions that as attractors, are central to sub-network organization. Here we provide the first application of a novel mathematical construction, Transitive Maximal Correlation (TMC) to task-driven data collected in schizophrenia patients. TMC was designed to identify a) regional attractors (by traversing the correlation landscapes that summarize cross-cerebral relationships between fMRI time series data, it is possible to identify an attractor pair that each region "flows" into) and b) regions that form the attractor basin for any attractor pair (Abdallah et al., In Revision, *PLoS Comp Biol*). We applied TMC to fMRI data (49, SCZ; 39, healthy controls) collected during an established learning task with four distinct task conditions (Nanaaware et al., 2025). Data were preprocessed using typical methods following which a full functional connectivity (FC) matrix (246 cerebral regions, 30,115 unique pairs)(Zhang et al., 2016) was estimated in each participant and condition. Each participant's TMC matrix was derived (for every node, we traverse a path of steepest ascent, i.e., most correlated neighbor, based on its local connectivity till the path converges on a pair of attractors). A "1" entry in a row of this binary TMC matrix indicates the identity of an attractor for the given region (each region converges on a pair of attractors; therefore, the sum of each row is two). Conversely, a "1" entry in a column indicates the identities of the regions that flow into that attractor (i.e., the attractor basin). Averaging TMC matrices across participants provides a measure of heterogeneity/homogeneity of regional attractors across the group. Here, non-zero values close to 0 indicate maximal *heterogeneity* whereas values close to 1 indicate maximal *homogeneity*. In each condition, Mann-Whitney U tests were used to compare inter-group differences in heterogeneity – homogeneity. Regardless of condition, SCZ showed greater heterogeneity in the identity of attractors to which region's converged (p-values: 4.4×10^{-19} to 2.3×10^{-25}), evidence of greater inter-subject variability in attractor identity and sub-network structure. Thus, TMC successfully recovers heterogeneity of functional network properties in schizophrenia.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.01/K2

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

Support: NIMH-IRP project number ZIC MH002903

Title: Cortical interneuronal circuitry inferred from scRNA-seq

Authors: L. HEINLY[1], P. NARNUR[2], A. SCHULMANN[3], G. S. SANTIAGO[4], Y. PATEL[2], D. KIM[5], P. K. AULUCK[6], Y. ZHANG[8], ***S. MARENCO**[7];
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Abstract: Background: Interaction pairs (IPs) of ligands and cognate targets are required for cell-to-cell communication (CCC). scRNA-seq enables the identification of cell type-specific IPs, allowing for inference of local connectivity patterns. We examined the local CCC of 19 interneuron subtypes conserved across mouse neocortex. **Methods:** We investigated 5 neocortical regions represented by 19 mice in the Yao et al. (2021) scRNA-seq dataset of adult mouse brain. We consolidated the original 57 interneuron clusters into 19 subtypes based on Spearman correlation of mean ligand and receptor expression across clusters, requiring at least 10 cells per cluster and animal. CellChat was used to calculate CCC probability for each IP. We measured variance in CCC explained by cell type pair, subject, or region. We performed clustering of cell type pairs in the reduced-dimensional space constructed by principal component analysis (PCA). **Results:** Cell type pair explained 73% of variance, while animal and region contributed < 2%, confirming that IPs are specific to circuitry between cell type pairs. PCA-based clustering identified 27 clusters demonstrating discrete connectivity between all interneurons, possibly consistent with the existence of recognition signals between all cell types. Cluster 4 had VIP, SNCG, and LAMP5 cell types (CGE-derived) as the senders and SST types as the receivers confirming the ability of the method to identify circuits that are known to be functionally relevant. LAMP5LHX6 cells acted as distinct senders in two clusters, one to all CGE-derived and the other to all MGE-derived cells, indicating they may be important regulators of coordinated activity between the two contingents. The three SST types appeared together as senders in 13 distinct clusters, indicating that differences in connectivity between SST subtypes and other interneurons are driven by afferent signals (receptor expression). SSTCHODL cells received the most diffuse input, receiving from all other interneurons in cluster 3. Chandelier cells also had diffuse input, receiving from all other interneurons in clusters 9, 12, and 20. CGE-derived cell types expressed many different interaction pairs and combined in complex ways, participating in 11 clusters as senders and 13 as receivers. **Conclusion:** We developed a CCC-defined connectivity map describing the dense circuitry between interneurons, partly consistent with previous functional studies. Some of the identified clusters can be thought of as putative circuits. We aim to extend these findings to the connectivity between other neuronal and non-neuronal cell types.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.02/K3

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

Support: NIH Grant R01NS105894
NIH R21 NS128635

Title: Corticothalamic NMDAR signaling shapes excitability in sensory thalamic networks

Authors: *R. KHONDAKER[1,2], M. LADISLAV[2], Y. CHEN[2], S. A. SWANGER[3,4];
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Abstract: The thalamus integrates peripheral sensory input with corticothalamic (CT) feedback from Layer 6 neurons to regulate sensory signal processing. Within the somatosensory thalamus, CT input differentially influences excitatory ventral posteromedial (VPM) neurons and inhibitory neurons of the thalamic reticular nucleus (nRT), which provide feed-forward inhibition to VPM. Yet the cellular and synaptic mechanisms governing this excitation-inhibition balance remain poorly understood. As N-methyl-D-aspartate receptors (NMDARs) possess unique biophysical properties that support synaptic integration, we aim to determine their cellular and synaptic contribution to CT-mediated signaling in VPM and nRT neurons. Acute thalamic slices from mice (P24-P28) expressing channelrhodopsin in Layer 6 CT neurons were used for optogenetic activation of CT afferents. CT-evoked spike firing and excitatory postsynaptic potentials (EPSPs) were recorded from VPM and nRT neurons under baseline conditions and during pharmacological blockade of NMDARs with pan-NMDA receptor antagonist D-2-Aminophosphonovaleric acid (D-APV). In parallel, multiplex fluorescent in situ hybridization (FISH) was used to examine NMDAR subunit expression in both nuclei. We identified that NMDAR blockade significantly reduced CT-evoked spike firing and EPSP amplitude in VPM neurons, indicating a substantial contribution of NMDARs to both cellular excitability and synaptic transmission. In contrast, nRT neurons exhibited comparatively smaller reductions in firing and EPSPs following D-APV application, suggesting reduced dependence on NMDAR-mediated signaling. Consistent with these physiological differences, VPM and nRT neurons displayed distinct NMDAR subunit expression profiles, with GluN2 subunits showing greater expression in VPM than in nRT neurons. Together, these findings reveal a cell-type-specific role for NMDARs in CT signaling and suggest that differential cellular and synaptic NMDAR recruitment in VPM and nRT neurons serves as a fundamental mechanism for regulating thalamic excitation-inhibition balance. **These findings establish a foundation for defining how GluN2 subtype-specific signaling shapes corticothalamic synaptic function and excitation-inhibition balance within sensory thalamic circuits.**

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.03/K4

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

Support: APVV 24-0391
APVV 19-0435
COST CA22114

Title: Maternal depression and antidepressant treatment: Consequences for offspring neurodevelopment

Authors: *K. ONDÁČOVÁ[1], A. FILIPOVÁ[2], M. TOMKO[1], L. NIEDEROVA-KUBIKOVA[3], S. BUKATOVA[4], L. LACINOVÁ[1];
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Abstract: Introduction: Maternal depression affects approximately 14-25% of women during the perinatal period and represents a significant risk factor for both maternal and offspring health. Prenatal stress and depression can adversely affect offspring brain development and lead to long-term neurobehavioral impairments. Although antidepressant treatment may alleviate maternal symptoms and reduce some adverse effects of maternal depression, its impact on the developing brain remains incompletely understood. **Aim:** To investigate the effects of maternal depression and mirtazapine treatment on hippocampal neuroinflammation and electrophysiology in offspring. **Methods:** Maternal depression was induced in female Wistar rats using a three-week chronic unpredictable stress (CUS) protocol prior to mating. Mirtazapine (10 mg/kg/day) was administered from gestational day 10 to postnatal day 13. Offspring were assigned to four groups: control-vehicle, control-mirtazapine, stress-vehicle, and stress-mirtazapine. Hippocampal microglial reactivity was assessed by Iba1 immunofluorescence, interleukin levels by ELISA, and neuronal excitability by whole-cell patch-clamp recordings in acute hippocampal slices. Analyses were performed in male and female offspring at postnatal days 10-13, representing early postnatal period. **Results:** Our results demonstrate reduced microglial reactivity in males in the group of offspring from stressed compared to non-stressed dams, an effect that was fully reversed by mirtazapine treatment. In females, the number of reactive microglia was significantly increased in the mirtazapine-treated group. Prenatal maternal CUS or mirtazapine treatment did not alter the expression of the inflammatory cytokine IL-6 in the hippocampus. Electrophysiological recordings showed that prenatal CUS facilitated neuronal excitability, as reflected by a reduced action potential (AP) threshold, a lower depolarizing current required to evoke single APs and AP trains, shortened AP latency, and faster AP rise time. Mirtazapine treatment only partially ameliorated stress-induced alterations in hippocampal excitability. **Conclusion**: Maternal stress altered hippocampal development by modulating neuronal excitability and microglial activity. Mirtazapine partially mitigated stress-induced changes and revealed sex-dependent effects, highlighting the need for further investigation. **Supported by APVV 24-0391, APVV 19-0435, COST CA22114.**

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.04/K5

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

Support: NIH R01NS115800
NIH P50 HD103556

Title: Cytotoxic edema is similar in neonatal and adult neocortical neurons but responds differently to hyperosmotic conditions.

Authors: *J. SMUSZKIEWICZ[1,3], J. GLYKYS[2];
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Abstract: Neuronal cytotoxic edema occurs after acute brain injury, such as strokes, seizures, and hypoxia, in both children and adults. Treatment for neuronal cytotoxic swelling includes hyperosmotic therapy to draw excess water out of cells. In clinical practice, hypertonic solutes include mannitol and sodium chloride (NaCl). However, whether neonatal and adult neocortical neurons swell to the same extent after excitotoxic injury, and whether mannitol or NaCl more effectively reduces neuronal swelling in each age group, remain unclear. We evaluated the extent to which a 20 mOsm increase in artificial cerebrospinal fluid (aCSF) induced by mannitol or NaCl decreases neuronal swelling in acute brain slices from Thy1-YFP mice (postnatal day P8-12 for pups, P60-90 for adults, both sexes) during and after 10 minutes of NMDA-induced excitotoxicity. Hypertonic solutions were perfused 10 minutes before, during, and after NMDA perfusion. Two-photon imaging showed that in pups and adults, NMDA perfusion increased neuronal area and caused slices to swell. After NMDA perfusion, neuronal size returned to baseline, but slice swelling persisted. There was no difference in the degree of neuronal or slice swelling between pups and adults. Mannitol decreased neuronal cell swelling during NMDA in pups and after NMDA in adults, whereas NaCl only decreased cell area after NMDA perfusion in adults. For slice swelling, mannitol reduced it during and after NMDA perfusion in pups and adults, while NaCl only decreased it during NMDA perfusion in adults. Mannitol was more effective during NMDA in pups and during washout in adults. We conclude that neonatal and adult neurons swell to the same extent after cytotoxic injury and that mannitol reduces neuronal cytotoxic edema and slice swelling in both age groups. By contrast, NaCl affected only adults. Therefore, although neonatal and adult neocortical neurons swell similarly, they respond differently to hyperosmotic conditions.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR299.05/K6

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

Support: NIH F31DA65413
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NIH R01DA43567
NIH R01NS140966

Title: Allosteric effects of lynx1 on α3β4 nicotinic receptor function are mediated by an accessory orthosteric site

Authors: *D. KNEISLEY[1,2], H. OH[3], Y. CAO[4], W. IM[4], J. M. MIWA[4], P. WHITEAKER[3]; [2]Dept. of Pharmacol. and Toxicology, [1]Virginia Commonwealth Univ., Richmond, VA; [3]Dept. of Pharmacol. and Toxicology, Virginia Commonwealth Univ., Henrico, VA; [4]Biol. Sci., Lehigh Univ., Bethlehem, PA

Abstract: Smoking, maintained by nicotine-seeking behaviors, is the world's leading cause of preventable death. Nicotine acts on nicotinic acetylcholine receptors (nAChR). The α3β4 nAChR subtype mediates aspects of nicotine withdrawal by modulating activity of GABAergic neurons of the interpeduncular nucleus. The prototoxin lynx1 is also highly expressed in these neurons, suggesting that lynx1 may play a role in nicotine withdrawal signaling. Lynx1 allosterically diminishes α3β4 macroscopic responses and is most potent on the $(\alpha3\beta4)_2\alpha3$ isoform, which uniquely contains an α3/α3 subunit interface. At the single-channel level, lynx1 decreases $(\alpha3\beta4)_2\alpha3$ conductance and shortens open bursts. Hence, we investigated the α3/α3 site for its role in lynx1 binding. Molecular dynamics simulations identified residues at the α3/α3 interface where lynx1 may interact; these were mutated in an alanine-scan. Sensitivity to lynx1 inhibition of the resulting mutants was assessed *via* two-electrode voltage clamp (TEVC) electrophysiology. These mutations were expected to decrease receptor sensitivity to lynx1, based on our hypothesis that lynx1 effects are mediated by this site. Several mutations did indeed show reduced lynx1 sensitivity. However, several other mutants showed enhanced lynx1 effects. Further, all mutant $(\alpha3\beta4)_2\alpha3$ exhibited diminished ACh-induced macroscopic function in the absence of lynx1. Combined, these observations support the recent finding of a third "accessory" agonist binding site at the α3/α3 interface, and further suggest that lynx1 and ACh compete to bind to it. Mutants with the most significant changes in lynx1 sensitivity from the TEVC studies were used for cell-attached single-channel patch clamp electrophysiology experiments to examine how mutations alter individual receptor function. Mutating a tyrosine residue in the α3/α3 interface, that corresponds to a critical agonist-binding residue in a conventional orthosteric binding pocket, reduced burst durations and single-channel amplitudes, *vs*. the wild-type (WT) receptor. These outcomes closely parallel those from our lab's previously published work of lynx1 binding to a WT receptor, further supporting the presence of a third ACh binding

site at the α3/α3 interface. Addition of lynx1 to the mutant receptor further reduced burst durations and single-channel amplitudes suggesting that, in addition to competing with agonist binding, lynx1 binding at the α3/α3 accessory orthosteric site may reduce the ability of the receptor to be activated by agonist binding at the two conventional orthosteric sites. The α3/α3 interface may be a promising target for new nicotine withdrawal therapies.

Disclosures: D. Kneisley: None. **H. Oh:** None. **Y. Cao:** None. **W. Im:** None. **J.M. Miwa:** None. **P. Whiteaker:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.06/K7

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

Support: DFG VI586
Graduate School of Life Sciences (GSLS) Würzburg

Title: Influence of the Neuroactive Steroids Allopregnanolone and Zuranolone on Inhibitory Neurotransmission and Synaptic Organization in the context of GlyR autoantibodies

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Abstract: Neuroactive steroids (NAS) are endogenously synthesized steroid hormones of the central nervous system (CNS). In particular, progesterone-derived NAS, such as allopregnanolone (Allo), are known to enhance the inhibitory transduction of γ-aminobutyric acid type A receptors ($GABA_ARs$). Allo and its pharmaceutical derivatives are used to treat depression-related neurophysiological disorders due to their known anxiolytic, antidepressant, and analgesic effects, as well as their advantageous therapeutic profile compared to the benzodiazepines. However, the influence of the NAS on neuronal activity, receptor function, and synaptic remodeling processes is not fully understood. We investigated the effects of the NAS Allo and Zuranolone on primary murine hippocampal and spinal cord neurons. Changes in overall neuronal activity are assessed by calcium imaging after application of NAS on primary neuronal cells, revealing differences between the modulatory strength of Allo and Zuranolone, while both compounds reduce the overall neuronal activity. Further structural and functional analysis of the effects of the NAS on different inhibitory receptor types was carried out through synaptic localization analysis in neurons and whole-cell patch-clamp recordings of transiently transfected HEK293 cells expressing synaptic and extrasynaptic subtypes of $GABA_ARs$ and GlyRs and neurons. While $GABA_ARs$ show distinct modulation by NAS, GlyRs remained largely unaffected. In addition, we investigated a potential compensatory effect of NAS on

inhibitory neurotransmission after pretreatment with patient-derived GlyR autoantibodies. GlyR autoantibodies are known to reduce glycinergic inhibition, specifically glycine potency. Our data thus far indicate that patient-derived autoantibodies induce an increase in excitation that can be partially counteracted by the application of NAS, highlighting their potential as pharmacological agents against neurological diseases affecting the inhibition-excitation balance.

Disclosures: J. Nausester: None. **M. Habib:** None. **S. Camuso:** None. **A. Pianos:** None. **C. Specht:** None. **C. Villmann:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.07/Web Only

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

Title: NACHO Mitigates Nicotine-Induced Reward:Insights into Nicotine Addiction

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Abstract: Nicotine is an exogenous substance known to exert its addictive effects by binding to nicotinic acetylcholine receptors located in the brain's reward pathway. The novel chaperone protein, NACHO, plays a critical role in the assembly, maturation, and surface expression of nicotinic receptors. However, NACHO's role in nicotine-induced reward is not yet fully understood. Our previous data suggests that age may affect NACHO expression in the ventral tegmental area, a brain region that plays a key role in mediating the rewarding effects of nicotine. Earlier this year, we conducted an experiment utilizing the conditioned placed preference behavioral test to further assess nicotine-induced reward in wildtype versus NACHO knockout mice. Following our hypothesis, wildtype subjects demonstrated a significant preference for the nicotine paired chamber compared to NACHO knockout subjects. To further examine the relationship between nicotine-induced reward and NACHO, we are now examining the activation of dopaminergic neurons in the ventral tegmental area between wildtype and NACHO knockout subjects.

Disclosures: A. Gonzalez: None. **K.A. Marquez:** None. **Y. Sherafat:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.08/K8

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

Support: This study was funded with a grant from the Global Action to End Smoking, Inc. ("Global Action"), a US nonprofit 501(c)(3) private foundation. Global Action had no role in the planning or execution of this study, data analysis, or publication.

Title: Drug repurposing screen of a library of FDA-approved compounds identifies multiple potential PAMs of alpha 7 nAChR: potential utility for nicotine use disorder.

Authors: *J. FARLEY[1], D. JAMSHIDI[2], J. HYATT[3], J. E. ROSE[4];
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Abstract: Tobacco use is a major public health concern; the most preventable cause of morbidity/mortality worldwide. Current FDA-approved tobacco smoking cessation medications [nicotine-replacement therapies (NRTs), varenicline, bupropion] increase the likelihood of long-term quitting ~ 2-3X vs. controls. But abstinence rates are only ~ 15-33% at 12 months. Thus, development of more effective treatments is critical. Tobacco use is reinforced by nicotine, that activates, desensitizes, and subsequently up/down-regulates neuronal nicotinic acetylcholine receptors (nACh Rs). nAChRs containing α4, β2, and α6 subunits have received the most attention, since these mediate the primary rewarding effects of nicotine. However, nAChRs containing the α7 subunit are also likely to contribute to reinforcement, withdrawal, and cue-induced relapse. α7* Rs have received much less attention as pharmacologic targets for smoking cessation. We are addressing this deficiency by moderate throughput screening of a library of FDA-approved compounds against homomeric α7 Rs expressed in oocytes with the aim of identifying potential positive allosteric modulators (PAMs) that could function analogously to NRTs. Murine α7 nAChR subunit cRNA was synthesized from a mα7 nAChR/pGEMHE plasmid. *Xenopus laevis* oocytes were injected with 1-2 ng of α7 cRNA. Functional expression of α7 Rs was evaluated 3-5 days post cRNA injection using TEVC & pClamp 10.2 at ~ 20 °C. A saturating concentration (500 μM) of ACh was used to elicit the α7 R at -60 mV in Negative Controls. The screening library contained a total of 3104 drugs. All drugs assessed were initially tested at 1 uM. Positive Control currents were obtained from same-batch oocytes exposed to ACh in the presence of well-established Type I & II PAMs [PNU 120596, 15 uM, or genistein, 100 uM]. Pos Control oocytes responded as expected, with PNU 120596- and genistein-exposed oocytes showing ~7-10X and ~4.6X greater peak currents than Neg Controls, respectively. We categorized the strength of facilitation effects (potential PAM action) of the various test compounds as follows: Weak (1.2 – 1.95X), Moderate (2.00 – 4.00X), Strong (> 4.25X). With these criteria, we identified 20, 16, and 3 distinct compounds as potential Weak, Moderate, or Strong PAMs, respectively. Because of their availability, brain penetrance, and dearth of reported adverse effects, two Moderate Facilitators were further characterized. Compounds A and B (so designated because of proprietary/IP issues) retained their facilitatory effects at a 0.01 uM concentration. We conclude that these compounds are potentially promising α7 PAMs for use in tobacco smoking cessation efforts.

Disclosures: J. Farley: 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 for drug study: “Pharmacotherapy Development for Smoking Cessation: Drug Discovery and Drug-Repurposing Studies for Select Nicotinic Acetylcholine Receptors (nAChRs)”. Rose Research Center LLC/, Rose Research Center LLC/"Global Action to End Smoking". **D. Jamshidi:** None. **J. Hyatt:** None. **J.E. Rose:** 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 for multiple drug and other studies concerning smoking cessation and nicotine dependence from NIDA; Global Action to End Smoking, Inc.;, Nicotine BRST LLC;, JUUL Labs; Altria; Embera Neurotherapeutics, Inc;, Otsuka Pharmaceutical; Swedish Match; Philip Morris International; Enorama Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent applications filed for bupropion/zonisamide and related drug combinations. Patent purchase agreement with Philip Morris International for nicotine inhalation system patents (final pay 2014). F. Consulting Fees (e.g., advisory boards); Phillip Morris International; JT International, SA.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.09/L1

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

Support: NIH 1R35GM162026

Title: ZZ161c Selectively Activates Human Homomeric α9 Nicotinic Acetylcholine Receptors

Authors: *L. AZAM[1], S. HEGDE[1], A. STARK[1], K. RICHTER[2], V. GRAU[2], J. M. MCINTOSH[1,3];
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Abstract: Nicotinic acetylcholine receptors (nAChRs) containing the α9 subunit occupy a distinctive position within the Cys-loop receptor superfamily. In contrast to the extensive pharmacology available for α7 nAChRs, α9-containing receptor pharmacology has remained comparatively underdeveloped despite growing interest in their role in auditory function, immune modulation and pain. Small-molecule antagonists for α9α10 receptors have been described for more than a decade, and more recent medicinal chemistry studies have identified small-molecule agonists of α9-containing receptors; however, those agonists also potently activate α9α10 heteromeric receptors rather than selectively activating homomeric α9 receptors. Accordingly, selective agonist activation restricted to α9 homomeric receptors has not been established. The present work describes a small molecule, ZZ161c, that can selectively activate

human homomeric α9 nAChRs expressed in *Xenopus laevis* oocytes. ZZ161c produced maximal agonist activity at 1 μM, yielding 70% of the response of a saturating concentration of acetylcholine (ACh). ZZ161c did not activate α7, α10, α9α10, or heteromeric neuronal nAChRs, including α4β2, α3β4, α3β2, or the muscle subtype at 1 μM. Very weak partial agonist activity was observed at high (100 μM) concentrations on α7 and α9α10 nAChRs (≈10% of the maximal ACh response for both subtypes). In contrast, ZZ161c blocked the effect of ACh on these nAChR subtypes at nanomolar concentrations, with IC_{50}s of 50 nM and 6.6 nM, respectively, with high nanomolar to low micromolar block of heteromeric nAChRs. Mutation of Tyr195 to Phe in the α9 orthosteric acetylcholine binding site reduced maximal ZZ161c agonist activity at α9Y195F homomeric receptors by 90% and completely abolished ACh activity. Interestingly, both ACh and ZZ161c were active on α9Y195Fα10 heteromeric receptors. However, the homologous mutation in the α10 subunit, α10Y192F, completely abolished agonist activity of ACh and the low affinity, weak partial agonist activity of ZZ161c on α10Y192Fα9 heteromeric receptors. Molecular
modeling yielded binding poses consistent with orthosteric engagement, with favorable agonist docking observed for α9 homomeric nAChRs, in accordance with high affinity agonism at α9+/α9-interface, and antagonist docking at the α10+/α9- interface. In cytokine release experiments, ZZ161c modulated release of Interleukin-1β, consistent with the presence of α7 and/or α9α10 nAChRs, but not α9 homomers. Together, these findings define a pharmacological profile that functionally separates α9 homomer activation from α9α10 receptor activation.

Disclosures: L. Azam: None. **S. Hegde:** None. **A. Stark:** None. **K. Richter:** None. **V. Grau:** None. **J.M. McIntosh:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.10/L2

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

Title: Resensitizers of nicotinic acetylcholine receptors - Promising antidotes for nerve agent poisoning

Authors: *K. V. NIESSEN[1], T. SEEGER[2];
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Abstract: Given the many conflicts worldwide, the possibility of chemical attacks cannot be excluded. Poisoning with organophosphorus compounds (OPCs), including nerve agents, remains particularly challenging, as available treatments are often insufficient due to limited accessibility and the rapid aging of several OPC-acetylcholinesterase (AChE) complexes. The AChE remains inhibited and the endogenous ligand acetylcholine accumulates in the synaptic cleft. Excessive binding of this agonist to muscarinic (mAChRs) and nicotinic acetylcholine

receptors (nAChRs) leads to overstimulation and in the case of nAChRs to desensitization, a dysfunctional receptor state. Without adequate treatment, this impaired signal transmission in the synaptic cleft manifests as a cholinergic crisis, ultimately leading to death via central and peripheral respiratory failure. Resensitizers for nAChRs are of particular interest as novel antidotes for normalizing receptor function and restoring muscle function. To identify possible nAChR resensitizers, computer aided drug design (CADD) in combination with *in-silico* modeling was applied. To gather structure-activity-relationship (SAR) data, radioligand binding assays and single channel measurement were performed. For both receptor affinity and functionality assays, purified membrane fragments containing 2αβδγ-nAChRs (muscle type), genetically homolog to the human adult 2α1β1δε muscle receptor, were used. Binding studies of bispyridinium, quinazoline, triazine and 3*H* indole compounds, derived from structure-based design syntheses, revealed binding to the orthosteric [^{3}H]epibatidine binding sites as well as the presumed allosteric MB327-PAM-1 binding site of the nAChR at varying affinities (pK_i 4.6 - 7.1 and pK_i 3.6 - 6.2, respectively) [1,2]. In single measurements, compounds exhibiting high affinity to the orthosteric binding sites showed no shift in charges due to Na^+ conduction, whereas compounds with affinity to the allosteric binding site were active. First data suggest that the mechanism of this resensitizing receptor interaction is probably that of a positive allosteric modulator (PAM) type II [3]. To summarize, nAChR resensitizers are promising new and effective antidotes for organophosphate poisoning. The acquired data, coupled with further information on receptor functionality, can be of great benefit in the development of a new therapy for nerve agent poisoning. [1] V. Nitsche et al., Toxicol. Lett., 392, (2024) 94-106 [2] T. Bernauer et al., Toxicol. Lett., 397, (2024) 151-162 [3] K.V. Niessen et al., Toxicol. Lett., 293, (2016) 190-197

Disclosures: K.V. Niessen: None. **T. Seeger:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.11/L3

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

Title: Novel receptor-active resensitizers as a potential therapeutic option for treating respiratory arrest caused by nerve agent poisoning

Authors: *T. SEEGER[1], K. V. NIESSEN[2];
[1]Bundeswehr Inst. of Pharmacol. & Toxicology, Munich, Germany; [2]Bundeswehr Inst. of Pharmacol. and Toxicology, Munich, Germany

Abstract: Poisoning with organophosphorus compounds (OPs) — including chemical warfare agents and certain insecticides — leads to a life-threatening cholinergic crisis caused by the inhibition of the vital enzyme acetylcholinesterase (AChE) and the resulting accumulation of acetylcholine. While overstimulation of muscarinic receptors (mAChR) can be effectively

treated with atropine, nicotinic receptors (nAChR) become dysfunctional due to desensitization. Treatment with oximes, which reactivate AChE, is ineffective in cases of poisoning by certain agents such as soman and tabun. Currently, there is no known drug therapy for direct intervention at the nAChR. Therefore, investigating receptor-active substances that reverse desensitization and thereby restore the function of the neuromuscular synapse and thus respiration would be an important strategy.To identify substances that restore neuromuscular function, diaphragm muscles of male Whistar rats were mounted on myographs and induced to contract via indirect electrical field stimulation (20 - 100 Hz). Muscle force was measured before and after the administration of soman, as well as after the application of various compounds (1-300 µM), and was evaluated as a time-force integral. Applying *in silico* studies based on the allosteric MB327 binding site on the nAChR, analogues of the lead structure MB327 [1] (pK_i = 3.4) with a 4-aminopyridinium ion substructure [2] (PTM0056 - PTM0072) with stronger binding were identified (pK_i 3.96 - 4.17). For the most part, these analogs exhibit a marked leftward shift in the concentration-response curve (up to 3 µM) and greater force recovery (30 - 50 % at 100 µM) in paralyzed muscles. However, these substances also demonstrate an inhibition of force recovery at higher concentrations. The quinazoline derivatives UNC0638, UNC0642, and UNC0646 also show very high binding strengths at the allosteric binding site, but only a weak restoration of muscle strength (0 - 18 % at 10 µM). Measurements performed on non-intoxicated muscle indicate that these substances also act as antagonists. In summary, all these substances facilitate force recovery in irreversibly inhibited respiratory muscles, thereby representing a promising, novel, and effective class of antidotes for organophosphate poisoning. Combined with further insights into receptor functionality, these data could make a significant contribution to the development of new therapies for nerve agent poisoning.[1] T. Seeger, et al., Toxicology 294 (2012) 80-84. [2] T. Bernauer, et al., Toxicol Lett, 397 (2024) 151-162 [3] V. Nitsche, et al., Toxicol Lett, 392 (2024) 94-106

Disclosures: T. Seeger: None. **K.V. Niessen:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.12/L4

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

Support: GSK (Ref: 25013464)

Title: Characterisation and antagonism of P2X3 current in human sensory neurons.

Authors: *I. M. OKOLIE[1,2], F. ESPINOSA[2], D. BAO[2], E. TANRIVER-AYDER[3], L. BENEDETTI[3], J. R. HOCKLEY[4], T. J. PRICE[5];
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Stevenage, United Kingdom; [5]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas Neurosci. Undergraduate Program, Richardson, TX

Abstract: Refractory chronic cough (RCC) is often considered a disease of neuronal hypersensitivity leading to excessive coughing. Camlipixant has shown benefit in reducing cough frequency in RCC patients through blockade of ATP signaling via selective P2X3 receptor antagonism, however, activity of camlipixant in primary human sensory neurons has not been investigated. In this study, we aim to characterize P2X3 receptor activity and inhibition using P2X3 antagonists in primary human sensory neurons. We have used human dorsal root ganglia (DRG) tissues, obtained by legal consent in the US, to prepare neurons by enzymatic dissociation. For calcium imaging, intracellular calcium levels were measured using Fluo-8 AM. For electrophysiology, gigaseals were generated prior to whole-cell voltage-clamp recordings. Repeated α,β-meATP (selective P2X3 agonist) applications were delivered in the presence of P2X3 receptor antagonists (either camlipixant or compound X) or control, and evoked calcium transients or currents measured. We find in both calcium imaging and electrophysiology experiments that ~50% of neurons were sensitive to α,β-meATP. Electrophysiological studies suggest that 46% exhibited current kinetics indicative of P2X3 with a rise constant of 163 ± 102 ms and decay constant of 1217 ± 265 ms (n=6), and high sensitivity to α,β-meATP. α,β-meATP-sensitive currents possessing different kinetics were observed, indicative of alternative P2X receptor subtypes. Camlipixant (at concentrations of 30nM and 300nM) consistently inhibited α,β-meATP-evoked calcium transients, and compound X (at 1μM) reversibly and selectively inhibited the majority of α,β-meATP-sensitive currents. In conclusion, our findings characterize P2X3 currents and show that camlipixant and compound X can selectively block P2X3 receptor activation in human sensory neurons.

Disclosures: I.M. Okolie: None. **F. Espinosa:** None. **D. Bao:** None. **E. Tanriver-Ayder:** A. Employment/Salary (full or part-time):; GSK. **L. Benedetti:** A. Employment/Salary (full or part-time):; GSK. **J.R. Hockley:** A. Employment/Salary (full or part-time):; GSK. **T.J. Price:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.13/L5

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

Support: ANR-23-CE16-0003

Title: Nucleus-specific regulation of oxytocinergic neurons by canonical and GluN3A-containing atypical NMDARs.

Authors: A. I. ARAYA MARTÍNEZ[1], *N. A. REBOLA[2];
[1]Fisiología, Inst. du Cerveau, Paris, France; [2]Paris Brain Inst., Paris Cedex 13, France

Abstract: Oxytocin regulates social behavior, stress responses, and neuroendocrine function. Oxytocinergic neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) release oxytocin from both axonal and somatodendritic compartments, with somatodendritic release thought to represent a major source of central oxytocin. Although this release is calcium dependent, the receptor mechanisms that regulate it remain poorly understood. NMDARs have long been considered strong candidate regulators, but their contribution to oxytocin release in vivo remains unclear. Recent evidence indicates that GluN3A-containing non-canonical NMDARs (GluN3ARs) can function as excitatory glycine/D-serine receptors in the brain and are mainly localized at extrasynaptic sites, suggesting that GluN3ARs may also regulate somatodendritic peptide release. Initial studies in GluN3A knockout mice suggest altered oxytocinergic function, yet the functional expression and role of these receptors in oxytocinergic neurons remain largely unknown.
Here, we investigated the role of canonical NMDAR and GluN3AR signaling in oxytocinergic neurons of the PVN and SON. Oxytocin neurons were identified in transgenic mice expressing Cre-dependent tdTomato under the oxytocin promoter. Whole-cell recordings in acute brain slices were combined with pharmacology and glycine or glutamate uncaging to assess synaptic and extrasynaptic currents mediated by GluN3ARs or canonical NMDARs.
Functional GluN3AR-mediated currents were detected in oxytocinergic neurons of both nuclei. Glycine uncaging evoked larger GluN3AR-mediated currents in SON neurons than in PVN neurons, indicating stronger GluN3AR-mediated responses in the SON. In contrast, glutamate uncaging revealed similar maximal NMDAR/AMPAR ratios in both nuclei, suggesting comparable levels of canonical NMDAR signaling in PVN and SON oxytocinergic neurons. Because D-serine acts both as an endogenous NMDAR co-agonist and as a ligand for GluN3ARs, we next examined its effects on synaptic and extrasynaptic NMDAR signaling. D-serine significantly potentiated extrasynaptic NMDAR currents in both nuclei. However, potentiation of synaptic NMDAR currents was observed only in SON neurons, whereas no significant effect was detected in PVN neurons.
These findings identify functional GluN3ARs in oxytocinergic neurons and reveal nucleus-specific regulation of synaptic and extrasynaptic NMDAR signaling in the PVN and SON. We are currently performing in vivo investigations to determine the contribution of both canonical and atypical NMDAR signaling to the control of oxytocinergic neurons and associated behaviors.

Disclosures: A.I. Araya Martínez: None. **N.A. Rebola:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.14/L6

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

Title: Search for positive allosteric modulators specific for the α3β2 nicotinic acetylcholine receptor

Authors: *S. N. SUDWEEKS[1], **S. ALVARADO-RUIZ**[2];
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Abstract: Nicotinic acetylcholine receptors are pentameric ligand-gated non-specific cation channels. The role of nAChRs in affecting cognitive diseases has driven researchers to explore its pharmacological potential by identifying molecules that act on specific nicotinic receptor subtypes. Due to the receptor's widespread distribution throughout the body and the brain, as well as its high degree of shared amino acid homology among different subtypes, it has proven a challenging target. Side-effects commonly occur with the administration of cholinergic transmission-altering compounds. For instance, encenicline a partial agonist of α7 nAChRs that was shown to improve learning and memory in animal models failed in clinical trials due to severe GI tract side-effects in human participants. Single-cell quantitative RT-PCR analyses performed by our lab using rat CA1 hippocampal interneurons, confirmed a notably strong presence of α3 mRNA expression, a surprisingly low expression of α4 mRNA, and an abundance of β2 mRNA in these neurons (in addition to the presence of several other nAChR subunits). Our data predicts that hundreds of neuronal nicotinic combinations are likely expressed in these neurons from the 11 nAChR subunits examined. Interestingly, since the α3β2 combination is not commonly found in either the PNS or the CNS, it may serve as a distinct target for CA1 hippocampal interneurons. Utilizing virtual docking and drug screening techniques, we aimed to identify allosteric modulators that would affect currents from the α3β2 nAChR subtype, with the goal of improving cognitive function in conditions such as Alzheimer's disease. Since no human α3β2 protein structure was readily available, we used SwissProt, AlphaFold, and ChimeraX to construct a α3β2 model, using the protein databank α4β2 files 6CNJ and 6CNK as the templates. We then used this α3β2 structure as a template for AutoDock Vina to screen using the ZINC database of chemical molecules to identify potential PAMs (positive allosteric modulators). After a list of potential drug candidates was generated, we compared their specificity between the α3β2, α4β2, and α3β4 nAChR subtypes. Here we report the results from the compounds with the greatest specificity tested *in vitro* using two-electrode voltage clamp with *Xenopus laevis* oocytes expressing nAChR subtypes.

Disclosures: S.N. Sudweeks: None. **S. Alvarado-Ruiz:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.15/L7

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

Support: RCHSS Internal Research Advancement Funds

Title: Blink: The regulation of associative learning through THC exposure and ACES

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Abstract: Prenatal THC exposure has been linked to disrupting the balance of GluN2A- and GluN2B-mediated NMDA receptor subunit expression leading to deficits in associative learning within rat subjects (Pinky et al. 2023). To extend these findings into humans, a translational model of eyeblink conditioning (EBC) was implemented. EBC is subdivided into two types: delay conditioning, which primarily involves cerebral learning circuitry, and trace conditioning, which additionally recruits forebrain circuitry. Due to differences in overall performance on EBC across developmental stages, our sample was limited to young adults ages 18-25 (Nicholson & Freeman 2000). Participants went through habituation trials that consist of exposure to both sound frequencies and the air puff. Next participants will have 5 alternating blocks of delay and trace conditioning (Cheng, et al. 2008), followed by extinction trials to measure differences in aspects of associative learning and how it is impeded. Participants complete a battery of self-report measures, including the BAM, MAST, STAI, CATS, DFAQ-CU, and ACEs questionnaires, to assess substance use, anxiety, cannabis use, and adverse childhood experiences. We hypothesize that higher ACE scores will be associated with impaired acquisition of conditioned responses and extinction rates during EBC. Additionally, we hypothesize that increased self-reported cannabis use will be negatively associated with the acquisition and performance of delay-conditioned responses. Lastly, Single nucleotide polymorphism (SNP) genotyping will be performed using quantitative polymerase chain reaction (qPCR) to determine if functional polymorphisms (rs180620, rs7301328, rs1070503, rs727605) in the GRIN2 gene further modify interactions in environment and cannabis use in eyeblink conditioning .

Disclosures: C.G. Parker: None. **E. Holliday:** A. Employment/Salary (full or part-time):; Kennesaw State University. **E. Clarke:** None. **E. Pogue:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.16/L8

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

Support: R35 GM162026
ZIC ES103326

Title: Probing the ligand-binding interface of human α7 nAChRs using cryo-EM and α-conopeptides

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[1]Univ. of Utah, Salt Lake City, UT; [2]George E. Wahlen Veterans Affairs Med. Ctr., Salt Lake City, UT; [3]California Inst. for Quantitative Biosci., Univ. of California Berkeley, Berkeley, CA

Abstract: The α7 nicotinic acetylcholine receptor (nAChR) is expressed by myriad nervous and non-nervous cell types and is a promising molecular target for treating pathologies including chronic pain, inflammation, and sepsis. Understanding how ligands interact with α7 nAChRs at the molecular level is important for designing highly selective drugs with minimal off target effects. We obtained a cryo-EM structure of the human α7 receptor bound to α-conopeptide [V11L,V16D]ArIB. We then used this ligand-receptor complex to identify pair-wise interactions between amino-acid residues predicted to be important for ligand potency. We assessed these interactions using electrophysiology of *Xenopus* oocytes expressing human α7 nAChRs and analogs of α-conopeptide PeIA with directed amino-acid substitutions designed to probe the chemical space of the ligand-receptor complex. These structure-activity relationship studies identified a single amino-acid substitution that conferred a ~275-fold increase in PeIA potency for α7 nAChRs. Further substitutions were made to create the analog PeIA-5454 that displayed >1,000-fold increase in potency relative to the native peptide. These studies define a set of critical ligand-receptor interactions that can be exploited to generate high-affinity drugs to target α7 nAChRs.

Disclosures: A.J. Hone: None. **K. Sharma:** None. **J. Gajewiak:** None. **L. Steed:** None. **J. McIntosh:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.17/M1

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

Support: NIH/NINDS R01NS115800
AES post-doctoral fellowship #1066027

Title: Contributions of GluN2A- and GluN2B-containing NMDA Receptors to Neocortical Excitability in the Neonate

Authors: *P. S. SURYAVANSHI[1], J. GLYKYS[2];
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Abstract: Excitatory transmission mediated by NMDA receptors (NMDARs) is essential for neurodevelopment, synaptic plasticity, and circuit function, whereas NMDAR dysfunction contributes to many neurological and psychiatric disorders. NMDAR function is strongly influenced by subunit composition, particularly GluN2 isoforms (A-D), which shape receptor biophysics and downstream signaling. In the neocortex, GluN2A/2B subunits predominate and undergo an early developmental shift from GluN2B- to GluN2A-containing receptors. However, the impact of this transition on excitotoxic pathology during early development remains unclear. We used subunit-specific inhibitors to examine the roles of GluN2A (TCN-201) and GluN2B

(Ro25-6981) in neuronal function and excitotoxicity in the developing neocortex of mice of both sexes at postnatal days 8-12. Both subunits contributed equally to NMDAR-mediated conductance, calcium transients, and susceptibility to spreading depolarizations. In contrast, only GluN2B inhibition mitigated persistent neuronal swelling and altered nuclear permeability, which are linked to lasting cellular and circuit dysfunction. Our results indicate that although NMDAR GluN2A and GluN2B contribute to physiological activity and the initiation of excitotoxic injury, GluN2B-containing receptors preferentially mediate subacute deleterious effects. In conclusion, our findings highlight the therapeutic potential of targeting GluN2B subunits to mitigate the subacute effects of neonatal excitotoxicity.

Disclosures: P.S. Suryavanshi: None. **J. Glykys:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.18/M2

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

Support: NIH Grant R35 GM138023
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NIH Grant T32 GM133369
NSF Cooperative Agreement No. OIA-2242771

Title: AMPA receptor maturation in the mouse auditory cortex is supported by synaptic zinc

Authors: *R. RUBY[1], K. BAINER[1], P. BENDER[1], C. T. ANDERSON[2];
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Abstract: The primary auditory cortex is crucial for the perception of sounds. This cortical area is highly enriched in synaptically released zinc, which acts as a potent modulator of cortical function and sound processing. Zinc (as Zn2+) is loaded into synaptic vesicles by the zinc transporter protein ZnT3, where it is coreleased with glutamate during synaptic transmission. When ZnT3 is constitutively knocked out of the mouse brain, there is a near complete loss of free zinc in synaptic vesicles. These ZnT3-knockout (KO) animals are a well-characterized tool for the study of synaptic zinc function and highlight the behavioral and physiological consequences of the loss of synaptic zinc. These KO mice exhibit hallmarks of synaptic immaturity, such as smaller dendritic spines and weaker synaptic connections compared to wildtype (WT) animals. Together these findings suggest that synaptically released zinc is important for normal synaptic maturation because ZnT3-KO mice retain immature glutamatergic receptors later into development than WT mice. We performed stereotaxic injections of retrograde tracer cholera toxin subunit B (CTB) Alexa 555 into the right inferior colliculus to fluorescently label pyramidal tract (PT)-type corticocollicular neurons in layer 5 of the auditory

cortex. Then, acute brain slices of the auditory cortex were prepared from the injected mice. Fluorescently labeled layer 5 corticocollicular neurons were targeted for whole-cell patch-clamping. We then used pharmacological techniques to characterize and identify different synaptic receptors at these synaptic connections. Glutamatergic synaptic events in the ZnT3-KO mice showed hallmarks of immature synaptic development. These physiological immaturities identify synaptic zinc as a key component in synaptic maturation, thus expanding the roles of synaptic zinc in brain development and brain function.

Disclosures: R. Ruby: None. **K. Bainer:** None. **P. Bender:** None. **C.T. Anderson:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.19/M3

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

Support: DoD NDSEG Fellowship
Wu Tsai Neurosciences Institute
Stanford Bio-X Interdisciplinary Graduate Fellowship

Title: Inverse Compression Ratio Detects Changes After Ketamine Exposure Across Species and Modalities

Authors: *A. TOR[1], Y. WU[1], P. NUYUJUKIAN[2];
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Abstract: The inverse compression ratio (ICR) is an information-theoretic measure that estimates the upper bound of the joint entropy of a signal using conventional compression algorithms. ICR has previously been used to detect epileptic seizure in qEEG data collected from humans (Yamada, et al., IEEE TBME 2025), as well as to detect electrolytic lesion in multielectrode array data collected from non-human primates (NHP) (Tor, et al., JNE 2026). Because ICR leverages data compression, it is well-suited to efficiently analyze heterogeneous datasets common to experimental neuroscience research. In this work, we apply ICR to open-source data to investigate the effect of ketamine, a common NMDA receptor antagonist, on neural data spanning several species and recording modalities. In particular, we investigate five combinations of species/modality: neuropixels (m-npx; n=8) and calcium imaging data (m-ca; n=8) from mice, LFP (n-lfp; n=2) derived from intracortical array data from NHP, and LFP (h-lfp; n=9) from EEG and fMRI (h-mri; n=43) data from humans. All data analyzed was from one minute before and one minute immediately after each subject received a dose of ketamine. Across all non-human datasets, lossless ICR (gzip) consistently increases after exposure to ketamine (Wilcoxon signed-rank: m-npx, m-ca, n-lfp: $p < 0.05$). On the other hand, lossy ICR (H.264) consistently nullifies or reverses this change (m-npx, m-ca, n-lfp: $p > 0.05$). These

results suggest that ketamine increases the overall randomness of neural data, increasing its losslessly estimated joint entropy. However, it may also rely on or activate simplistic mechanisms which result in temporal redundancies that are identified by lossy compressors. Furthermore, these multi-species and multi-modality results also suggest that the effects of ketamine on neural activity are significant and global, reflecting the ubiquity of NMDA receptors across the mammalian brain. In both human datasets, lossless ICR does not exhibit any consistent statistically significant change. This may be because of limitations of noninvasive methods used to collect these datasets. Information-theoretic analyses, like ICR, may be used as a convenient and efficient tool to characterize changes in neural data that may otherwise be difficult to identify with statistically complex methods.

Disclosures: A. Tor: None. **Y. Wu:** None. **P. Nuyujukian:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.20/M4

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

Support: NIH Grant R35GM137951
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NIH Grant R21NS146672

Title: Adapting to Channel Topology: Engineering Tags for the Study of ASIC Trafficking

Authors: *A. MOUSAEI, D. M. MACLEAN;
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Abstract: Acid-sensing ion channels are acid-activated trimeric ion channels widely expressed throughout the body. Activated by extracellular protons, ASICs respond to acidification by transmembrane ion flux. They have been implicated in diverse physiological and pathological processes, including learning and memory, synaptic plasticity, fear conditioning, pain, and ischemic stroke. However, the mechanisms by which ASICs contribute to these processes remain incompletely understood. In particular, how differences in ASIC trafficking contribute to pathological conditions is poorly explored, in large part because methods to directly, robustly, and easily quantify ASIC surface expression are limited. Split-luciferase systems such as NanoBiT, where an exogenously supplied Large Bit (LgBiT) combines with a high-affinity peptide (HiBiT) encoded in the protein to form a functional nanoluciferase, provide a powerful approach for measuring surface versus total protein levels. However, ASICs are not amenable to such assays as their N and C termini are intracellular.
Here, we engineered HiBiT insertions into the human ASIC1a extracellular domain to identify positions that tolerate tagging while preserving channel function. Ideal insertion sites should maintain trafficking properties and gating properties similar to wild-type ASIC1a. We screened a

series of HiBiT insertion positions for current density followed by pH sensitivity and channel kinetics, finding two promising positions. Because HiBiT/LgBiT complementation requires association of LgBiT with the receptor-provided HiBiT tag, the inserted tag must be sufficiently accessible. Our initial constructs showed slower association times, suggesting limited accessibility for LgBiT binding. To improve complementation efficiency and reduce potential strain on the protein fold, we tested flexible, rigid, and hybrid linkers flanking the HiBiT sequence, followed by additional testing. Through this iterative screening approach, we isolated the strongest candidate. ASICs have an especially cooperative activation with multiple suggested proton-binding sites and any changes in the channel structure are bound to affect its properties. Yet, our final design only had an estimated 22.2% decrease in the whole cell current, and right-shifted activation pH_{50} by 0.14 pH units.
This optimized HiBiT-tagged ASIC1a construct provides a new tool for studying ASIC1a trafficking and surface expression while preserving key functional properties of the channel. In the future, additional tags and modifications can be added to the sites we screened, providing further tools for studying these channels.

Disclosures: A. Mousaei: None. **D.M. MacLean:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.21/N1

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

Support: CIHR Foundational Grant to BAO
University of Toronto Connaught Fund

Title: Surgery remodels inhibitory neurotransmission and promotes astrocytic reactivity in mouse hippocampus

Authors: *H. Y. FANG[1], M. YU[1], Y. ZHANG[1], D.-S. WANG[1], J. BA[1], C. T. BRENNA[1], L. KAUSTOV[2], B. A. ORSER[3];
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Abstract: Perioperative neurocognitive disorders (PNDs) are common complications of surgery, yet their mechanisms remain poorly defined. $GABA_A$ receptors containing α5 subunits ($\alpha5GABA_ARs$) are increasingly recognized as important contributors to PNDs. These extrasynaptic receptors are enriched in hippocampal neurons where they mediate a tonic inhibitory conductance that regulates cognition. Surgery increases $\alpha5GABA_AR$ surface expression and causes cognitive deficits that are mitigated by $\alpha5GABA_AR$-selective inhibition. Moreover, we have also shown that general anesthetic drugs trigger astrocytes to release soluble

factors that enhance tonic inhibitory currents in hippocampal neurons. However, the effects of surgery on α5GABA$_A$R transcription, translation, inhibitory signalling, and astrocytic phenotype in the hippocampus have not been systematically and concurrently characterized *in vivo*. Adult mice underwent laparotomy under sevoflurane anesthesia. Hippocampal tissue was collected 72 h later for Western blotting, surface biotinylation, and RT-qPCR. Whole-cell voltage-clamp recordings from CA1 pyramidal neurons assessed miniature inhibitory postsynaptic currents (mIPSCs), current noise, and tonic inhibition. Perfusion-fixed brain sections were immunolabelled for glial fibrillary acidic protein (GFAP), imaged by confocal microscopy, and analyzed for astrocytic reactivity and arbourization using Sholl analyses. We found that surgery increased total and surface α5 subunit protein, *Gabra5* mRNA, current noise, and tonic inhibitory current amplitude. In contrast, mIPSC charge transfer was reduced and decay kinetics were accelerated. Further, astrocytes were hypertrophied with greater GFAP fluorescence intensity, and Sholl analyses revealed increased distal arbourization and morphological complexity. Together, our findings show that surgery induces transcriptional and translational upregulation of hippocampal α5GABA$_A$Rs, enhances tonic inhibition, weakens synaptic inhibitory signalling, and promotes astrocytic reactivity. The reduction of synaptic inhibition suggests potential internalization or lateral movement of α5GABA$_A$Rs to extrasynaptic domains. Surgery-induced dysregulation of astrocytes may further enhance hippocampal tonic inhibitory signalling through the release of soluble factors and represents a promising therapeutic target for PNDs.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.23/N3

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

Support: NIH grant NS132590
NIH grant NS118731
NIH grant NS133338
NIH grant MH116003

Title: Activation of glutamate delta 1 receptor by acetylcholine

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and neuroscience, Texas A & M Univ., College Station, TX; [4]Psychiatry and Behavioral Sci., Texas A&M, College Station, TX; [5]Pharmacol. and Neurosci., Creighton Univ., Omaha, NE; [6]Emory Univ., Atlanta, GA; [7]Univ. of Wisconsin, Madison, WI; [8]Emory Primate Center, Dept Neurol., Emory University, Emory Natl. Primate Res. Ctr., Atlanta, GA

Abstract: The GluD1 receptor has many unusual features including expression at both excitatory and inhibitory synapses and a ligand binding domain capable of binding both D-serine and GABA. Nonetheless, these ligands do not induce ion channel activity in cellular context. We found that GluD1 is enriched postsynaptically at cholinergic synapses in the mouse and monkey dorsal striatum raising the possibility of acetylcholine could serve as a ligand for GluD1. We found that optogenetic stimulation of cholinergic interneurons or puff-application of ACh, in the presence of cholinergic and AMPA/GABAA receptor blockers, produced current responses in medium spiny neurons (MSNs) that were sensitive to the GluD1-channel blocker NASPM. These responses were absent in GluD1 KO and overexpression of GluD1 on KO background rescued Ach puff-induced currents suggesting potential conductance via GluD1. Finally, using Cbln1 displacement assay as an indirect method to evaluate ligand binding interaction, we found that ACh can bind GluD1 and induce conformational changes. A similar ACh-induced conformational change was observed for GluD2 in the cell binding assay. Importantly, molecular dynamics simulations and mutagenesis analysis demonstrated that ACh binding orientation in the GluD1 ligand binding domain is different from D-serine and GABA. Our current data and follow up studies identify a unique mechanism of activation of GluD1 by acetylcholine.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.24/N4

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

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

Title: Novel K2060 derivatives and their role in the membrane-to-channel inhibition of NMDA receptors

Authors: *J. NETOLICKY[1], M. KOLCHEVA[2], M. LADISLAV[3], M. HORAK[4];
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Abstract: N-methyl-D-aspartate receptors (NMDARs) are ligand-gated ion channels essential for excitatory neurotransmission, synaptic plasticity, learning, and memory, and their

dysfunction is implicated in epilepsy, Alzheimer's disease, and GRIN-related neurodevelopmental disorders. We previously identified K2060, a reversible MK-801-derived NMDAR open-channel blocker with prominent membrane-to-channel inhibition (MCI) and favorable central nervous system (CNS) drug-like properties. Here, we hypothesized that MCI of K2060 derivatives is associated with inhibitory potency, expressed as IC_{50}, and physicochemical properties, including predicted pK_a and logD. We therefore designed and characterized a series of more than 20 novel K2060 derivatives to test the relationships between MCI and IC_{50}, predicted pK_a, and predicted logD. New analogues were synthesized by modifying the cyclobutylamine moiety, aromatic region, and cycloheptenyl core of K2060. Activity was evaluated by whole-cell patch-clamp recordings from HEK293 cells expressing recombinant human GluN1/GluN2A receptors at −60 mV, using glutamate-evoked currents to determine relative inhibition, concentration-response relationships, and MCI. Initial screening at 1 μM identified K2961, K3523 and K3543 as the most active compounds, each producing more than 50% inhibition of NMDAR-mediated currents. Concentration-response analysis showed that K3523 and K2961 had the lowest IC_{50} values, 0.49 ± 0.04 μM (n = 6, mean ± SEM) and 1.07 ± 0.07 μM (n = 4), respectively, while K3543 had an IC_{50} of 2.47 ± 0.42 μM (n = 5). Using a standard MCI protocol, the strongest MCI was observed for compounds with the lowest IC_{50} values, including K2961, K3523, and K3543. Pearson's correlation analysis showed no clear association between MCI and predicted logD ($R^2 = 0.19$, $r = -0.44$, $p = 0.23$) or predicted pK_a ($R^2 = 0.02$, $r = -0.04$, $p = 0.91$), whereas MCI was strongly associated with IC_{50} values ($R^2 = 0.87$, $r = 0.93$, $p = 0.001$). Several selected compounds showed predicted blood-brain barrier permeability and favorable plasma or microsomal stability. Together, these data identify potent K2060-derived NMDAR antagonists and indicate that IC_{50}, rather than predicted pK_a or logD, is the main parameter associated with MCI within this compound series.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.25/N5

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

Support: Czech Health Research Council Grant NW24J-04-00084
MEYS CR ExRegMed Grant CZ.02.01.01/00/22_008/0004562

Title: GRIN2A-N615S removes Mg^{2+} control of ketamine potency and onset while preserving enantiomer-specific offset

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Abstract: NMDA receptors (NMDARs) are essential for synaptic signaling, and pathogenic GRIN2A variants can disrupt ion permeation and channel block. The GluN2A-N615S pore substitution markedly reduces Mg^{2+} sensitivity, suggesting that it may alter inhibition by open-channel blockers such as ketamine. We first tested racemic ketamine on recombinant GluN1/GluN2A and GluN1/GluN2A-N615S receptors using whole-cell patch-clamp recordings in HEK293 cells. In WT receptors, 1 mM Mg^{2+} shifted racemic ketamine potency from 0.49 ± 0.06 μM to 7.32 ± 0.22 μM and slowed onset at 10 μM from 168 ± 9 ms to 531 ± 59 ms, consistent with concentration-dependent channel block. In contrast, N615S receptors remained highly sensitive in Mg^{2+}, with IC_{50} values of 0.48 ± 0.06 μM in 0 Mg^{2+} and 0.44 ± 0.03 μM in 1 mM Mg^{2+}, and showed little Mg^{2+}-dependent slowing of onset: 179 ± 30 ms vs 234 ± 20 ms. Racemic ketamine offset was only weakly affected by Mg^{2+}, indicating that Mg^{2+} primarily modifies potency and onset rather than recovery. Acute hippocampal slices confirmed stronger and faster ketamine inhibition in N615S synaptic NMDARs. We next tested individual ketamine enantiomers. In Mg^{2+}-free conditions, S- and R-ketamine inhibited WT receptors with IC_{50} values of 0.40 ± 0.04 μM and 0.79 ± 0.11 μM, respectively. N615S produced similar values: 0.41 ± 0.06 μM for S-ketamine and 0.76 ± 0.12 μM for R-ketamine. In WT receptors, 1 mM Mg^{2+} shifted enantiomer potency to higher concentrations, with IC_{50} values of 5.06 ± 0.56 μM for S-ketamine and 16.53 ± 0.93 μM for R-ketamine. In N615S receptors, this Mg^{2+}-dependent loss of potency was largely absent, with IC_{50} values of 0.48 ± 0.07 μM and 0.79 ± 0.15 μM for S- and R-ketamine, respectively. Kinetic analysis showed that Mg^{2+} slowed onset for both enantiomers in WT receptors. At 10 μM, S-ketamine onset slowed from ~194 ms to ~896 ms, and R-ketamine onset slowed from ~432 ms to ~1093 ms. This effect was strongly reduced in N615S receptors. Because ketamine onset was concentration-dependent, Mg^{2+}-dependent slowing in WT may partly reflect the rightward potency shift. In contrast, recovery was governed mainly by the enantiomer: S-ketamine washed out within ~4.4-5.1 s, whereas R-ketamine recovered within ~1.5-2.0 s. This 2-3-fold offset difference was preserved in N615S receptors and was not detectably modified by Mg^{2+}. Together, GRIN2A-N615S abolishes Mg^{2+}-dependent modulation of ketamine potency and onset while preserving enantiomer-specific offset kinetics. Reduced Mg^{2+} block may therefore enhance ketamine sensitivity in GRIN-related disorders, whereas distinct R/S washout kinetics may shape the duration of NMDAR inhibition.

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Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.26/N6

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

Support: NW24-04-00412

Title: Methoxphenidine metabolites differentially inhibit GluN2A- and GluN2B-containing N-methyl-D-aspartate receptors through voltage-dependent open-channel block and membrane-to-channel inhibition

Authors: *M. KOLCHEVA, M. LADISLAV, J. NETOLICKY, M. HORAK;
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Abstract: Methoxphenidine (MXP) and related diarylethylamines are noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonists with therapeutic potential, but the mechanisms underlying their receptor inhibition remain incompletely understood. Here, we examined how stereochemistry and structural variation within MXP-related compounds affect NMDAR inhibition by comparing R-MXP, S-MXP, 4OH-MXP, and dmMXP using electrophysiological recordings from GluN1/GluN2A and GluN1/GluN2B NMDARs. Concentration-inhibition relationships were measured at -60 and +40 mV for GluN1/GluN2A and GluN1/GluN2B NMDARs, onset/offset kinetics and membrane-to-channel inhibition (MCI) were analyzed for GluN1/GluN2A NMDARs. At -60 mV, R-MXP showed the lowest potency and moderate GluN1/GluN2B preference (0.89±0.12 vs. 0.44±0.01 μM for GluN2A and GluN2B; mean±SEM), whereas S-MXP was more potent (0.46±0.06 vs. 0.27±0.08 μM for GluN2A and GluN2B). 4OH-MXP and dmMXP showed little subunit selectivity, with IC_{50} values of ~0.3 and ~0.4 μM for GluN2A and GluN2B, respectively. Depolarization reduced potency for all compounds, consistent with voltage-dependent open-channel block; however, dmMXP retained the highest potency at +40 mV for both GluN1/GluN2A and GluN1/GluN2B receptors, with IC_{50} values of ~4 μM for both receptor subtypes. In contrast, the other compounds showed larger rightward shifts in IC_{50}, particularly for GluN1/GluN2A receptors, with values in the range of 25-58 μM. Kinetic analysis showed concentration-dependent acceleration of block onset for all compounds, as expected for classical open-channel blockers, whereas recovery from block differed markedly among compounds - R-MXP washed out rapidly (~5 s), S-MXP and 4OH-MXP recovered more slowly (~20 s), and dmMXP showed very slow offset (~70 s). MCI analysis further separated the derivatives: at 10 μM, 4OH-MXP showed only weak membrane-mediated inhibition ($I_{MCI}/I_{Control}$ = 0.86±0.01), consistent with predominantly classical open-channel block, whereas R-MXP, S-MXP, and dmMXP showed lower MCI values ($I_{MCI}/I_{Control}$ = 0.55±0.06, 0.39±0.04, and 0.42±0.03), indicating stronger membrane-mediated inhibition. Together, these results show that MXP derivatives are potent voltage-dependent NMDAR blockers with distinct recovery kinetics and MCI. The slow recovery and strong membrane-mediated component of dmMXP may prolong NMDAR inhibition, identifying these properties as important parameters for further optimization of MXP-derived NMDAR antagonists.

Disclosures: M. Kolcheva: None. **M. Ladislav:** None. **J. Netolicky:** None. **M. Horak:** None.

Poster

PSTR299: Ligand-Gated Receptors and Ion Channels

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR299.27/N7

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

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

Title: Calpain 1-mediated proteolysis of G3BP1 links NMDAR activation to mTOR-dependent local translation

Authors: *S.-Y. AHN[1,2], D.-H. PARK[1,2], Y. SUH[1,2];
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Abstract: Local protein synthesis in neurons plays a critical role in synaptic plasticity, neuronal remodeling, and axonal regeneration, and is tightly regulated by ribonucleoprotein (RNP) granules that sequester translationally repressed mRNAs. Although the disassembly of RNP granules is required to reactivate translation, the mechanisms that couple neuronal activity to this process remain unclear.
Here, we show that N-methyl-D-aspartate receptor (NMDAR) activation induces calcium influx, triggering calpain 1 to proteolytically cleave Ras-GTPase-activating protein-binding protein 1 (G3BP1). Mechanistically, calpain 1 constitutively interacts with G3BP1 and cleaves its proline-rich intrinsically disordered region (IDR2), resulting in the disassembly of G3BP1-positive granules in neurites.
Functionally, cleavage of G3BP1 enhances mTOR-dependent local translation, thereby linking synaptic activity to spatially restricted protein synthesis. Moreover, we demonstrate that this NMDAR-calpain 1-G3BP1-mTOR signaling axis promotes axonal regeneration following neuronal injury. Together, our findings identify proteolytic remodeling of RNP granules as a key mechanism by which neuronal activity controls local translation to support neural repair.

Disclosures: S. Ahn: None. **D. Park:** None. **Y. Suh:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.01/N8

Topic: B.05. Synaptic Plasticity

Support: RS-2021 -KH112574

Title: Arc release plays a crucial role for synaptic plasticity and memory decline due to oAβ deposits in Alzheimer's disease

Authors: *S. KIM[1], Y. LEE[2], S. KIM[3];
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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive memory decline and cognitive impairments. Neurological & Psychiatric Disorders such as Abnormal levels of Arc in blood exosomes are investigated as potential peripheral biomarkers for conditions like temporal lobe epilepsy, Alzheimer's disease, and autism spectrum disorders. Arc (Activity-Regulated Cytoskeleton-Associated Protein) plays a critical role in synaptic plasticity, learning, and memory. Therefore, AD is considered a "synaptopathy" where high levels of Amyloid-β (Aβ) provoke Arc leakage. A product of the immediate early gene Arc (Activity-regulated cytoskeleton-associated protein or Arc protein) of retroviral ancestry resides in the genome of all tetrapods for millions of years and is expressed endogenously in neurons. It is a well-known protein, very important for synaptic plasticity and memory consolidation. Researchers use methods like immunocapture to isolate neuron-specific extracellular vesicles (NEVs) from blood plasma.Immunoassays & Mass Spectrometry: Researchers use specialized Arc ELISA Kits to measure levels as low as < 0.059 ng/mL. High-sensitivity western blotting and mass spectrometry are also used to detect and confirm Arc oligomers. In this work has recently demonstrated that the memory gene Arc controls the expression of most genes involved in the pathophysiology of AD and a reusable aptamer-based on QD probe for the detection of oAβ and Arc has been developed. This discovery suggests a new direction for drug development to create more effective treatments that can be effective in the early stages of Alzheimer's disease. Since Arc plays a crucial role in regulating the expression of various genes and memory loss pathways involved in the pathophysiology of Alzheimer's disease induced by oAβ, it can be a key research subject for the development of effective treatments.

Disclosures: S. Kim: None. **Y. Lee:** None. **S. Kim:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.02/O1

Topic: B.05. Synaptic Plasticity

Support: National Institutes of Health, R01NS106031, R01NS113079, R01MH135141
Life Sciences Research Foundation
Vallee Foundation
MathWorks

Title: Dendritic plateau potentials are instructive signals for rapid neocortical plasticity

Authors: *C. E. YAEGER[1], R. MOJICA SOTO-ALBORS[2,1], A. L. BELTRAMINI[1], M. T. HARNETT[2,1];
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Abstract: Learning requires adjusting synaptic weights across a variety of timescales, from single-shot changes to iterative refinement. The prevailing model in the neocortex, spike-timing dependent plasticity, requires many repetitions of precisely coordinated activity that is difficult to reconcile with rapid learning commonly observed in behaving animals. In hippocampus, an alternative form of plasticity driven by plateau potentials (behavioral timescale synaptic plasticity; BTSP) alters synaptic weights in a single trial to reorganize spatial representations and drive learning. Here we show that layer 5 pyramidal neurons (L5 PNs) of mouse primary visual cortex (V1) exhibit highly prevalent plateau potentials that drive single-shot changes in sensory representations. Inhibiting L5 PN apical dendrites decreases plateau prevalence, and suppressing these signals in V1 during task performance disrupts the learning of a novel visual cue-reward association. In acute slices, plateau potentials drive synapse-specific plasticity with few repetitions across seconds-long pairing intervals. Our results demonstrate that plateau potentials in neocortex rapidly reshape neuronal representations through BTSP, a mechanism for dynamic adjustment of neocortical synaptic weights that enables rapid learning.

Disclosures: C.E. Yaeger: None. **R. Mojica Soto-Albors:** None. **A.L. Beltramini:** None. **M.T. Harnett:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.04/O3

Topic: B.05. Synaptic Plasticity

Support: F31EY036749
R01EY014882

Title: Pathway Specific Eligibility Traces: Reinforcement-like Plasticity in the Visual Cortex

Authors: *C. WESSELBORG[1], H.-K. LEE[2], A. KIRKWOOD[3];
[1]Biol., [2]Neurosci., [3]Mind Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Coincident pre- and post-syanaptic activity is the basis of Hebbian plasticity implicated in learning and memory. However, it has been recognized that behaviorally relevant feedback information conveying saliency and valance, is often delayed on the order of seconds following the coincident neural activity. Therefore, Hebbian mechanism alone is insufficient to account for reinforcement-based learning in organisms. To address this gap, it has long been proposed that active neurons are eligible for synaptic modification during a short window after activity has occurred. One proposal is via generation of an eligibility trace or eTrace. An eTrace alone is silent and transient, and only when a delayed feedback signal arrives within its transient

time window does synaptic modification occur. Experimental evidence of eTraces has been described recently in several brain regions indicating a common and widespread mechanism for reinforcement-like learning on behavioral timescales. In our previous work, we demonstrated that delayed neuromodulators, norepinepherine (NE) and serotonin (5-HT), are responsible for converting eTraces to express synaptic plasticity in the mouse primary visual cortex (V1) at the feedforward Layer 4 to Layer 2/3 pathway (L4 to L2/3). Neurons, however, from extensive connections representing input from functionally diverse brain regions, whether such neuromodulator-dependent eTraces are universal across all synapses or are limited to a subset has not been established. Here we investigated the pathway specificity of eTraces using whole-cell patch-clamp electrophysiology by recording from L2/3 pyramidal cells while stimulating two independent pathways: feedforward L4 to L2/3 and lateral intracortical L2/3 to L2/3 connections. We demonstrate that NE and 5-HT coupled eTraces in V1 are not universally expressed, but rather, are restricted to feedforward connections. Furthermore, we found that the intracortical pathways, still capable of plasticity, express a distinct eTrace mechanism dependent on the cholinergic system, which is not found in the feedforward pathway. Our results support a novel view that distinct information streams in V1 are modified by behavioral-timescale reinforcement-like mechanisms coupled to distinct neuromodulatory signals.

Disclosures: C. Wesselborg: None. **H. Lee:** None. **A. Kirkwood:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.05/O4

Topic: B.05. Synaptic Plasticity

Support: NIH R21MH135232-01A1

Title: The GluN2B CTD permits the induction of ionotropic and nonionotropic NMDAR-dependent synaptic long-term depression in the hippocampus

Authors: *L. C. MCAULIFFE, E. B. WRIGHT, T. C. DUMAS;
George Mason Univ., Fairfax, VA

Abstract: N-methyl-D-aspartate receptors (NMDARs) drive lasting changes in synaptic efficacy through calcium-dependent (ionotropic) and calcium-independent (nonionotropic) mechanisms. Activity-dependent weakening of synaptic strength (long-term depression, LTD) mediated by NMDARs is more easily induced in the immature hippocampus than the mature hippocampus. The developmental shift in LTD induction threshold occurs in parallel with a shift in NMDAR subunit composition from GluN2B to GluN2A predominance, such that as the number of synaptic GluN2A-containing NMDAR increases, LTD becomes harder to induce. While nonionotropic NMDAR-dependent LTD has been studied primarily in juvenile rodents, developmental regulation has not been directly investigated. Given that nonionotropic spine

shrinkage is dependent on the GluN2B carboxy terminal domain (CTD), we hypothesized that reduced GluN2B CTD signaling resulting from the GluN2B to GluN2A shift is responsible for the decrease in LTD expression. We tested this hypothesis by recording field excitatory postsynaptic potentials in hippocampal slices acutely prepared from transgenic mice expressing chimeric GluN2 subunits (CTDs swapped between GluN2A and GluN2B, termed GluN2A-B^{CTD} and GluN2B-A^{CTD}), which permit experimental separation of ionotropic and nonionotropic signaling. Half of the slices were perfused with artificial cerebrospinal fluid (ACSF) and the other half with ACSF containing MK-801 to block ionotropic NMDAR signaling. Before the GluN2B to GluN2A shift at postnatal days (P) 17-19, LTD was induced by low-frequency stimulation (LFS, 1 Hz for 15 minutes) in all slices except those collected from GluN2B-A^{CTD} mice. After the GluN2B to GluN2A shift at P22-24, LTD was only induced in GluN2A-B^{CTD} mice. When MK-801 was applied, LTD magnitude increased in slices from GluN2A-B^{CTD} mice at P17-19 but decreased at P22-24. Additionally, paired-pulse facilitation was increased in all cases that LTD was induced, suggesting a lasting reduction in transmitter release contributes to ionotropic and nonionotropic LTD. These data show ionotropic and nonionotropic LTD are positively regulated by the GluN2B CTD, and nonionotropic LTD is most prevalent before the subunit shift. Results from this study further our understanding of LTD on the level of individual NMDAR subunit domains, allowing for a more complete understanding of hippocampal maturation and potentially better therapeutics for various psychiatric disorders.

Disclosures: L.C. McAuliffe: None. **E.B. Wright:** None. **T.C. Dumas:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.06/O5

Topic: B.05. Synaptic Plasticity

Support: NIMH R01MH128344
NIMH R01MH110594
NIMH R01MH116937

Title: Sleep Replay Constructs Novel Rewarded Routes

Authors: *R. AALISHAH[1], A. HATAMI[1], I. E. MONOSOV[2];
[1]Dept. of Electrical and Computer Engin., [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Offline replay is usually studied as a way to strengthen or reorganize past experience. We asked whether replay can instead build a behavioral route that was never taken while awake. We tested this in a spiking neural network (SNN) trained on a navigation task with hidden reward at interior nodes. The network was built from leaky integrate-and-fire units arranged as a four-layer feedforward graph. The reward-optimal route to the goal ran through two synaptic connections whose weights were too weak to drive postsynaptic spiking, so waking behavior

could reach parts of the route but never capture the full optimal route. Waking trials used spike-timing-dependent plasticity (STDP) for learning and produced route fragments to be replayed later during sleep. We tested two ways replay might strengthen the missing connections. First, membrane-noise variance in the replay dynamics started high and annealed to low variance over each sleep period, so replay sampled variable trajectories early and stabilized stronger ones later. Second, two fragments were reactivated close together in time so that STDP could potentiate the connection between them. Each manipulation strengthened the initially subthreshold connections and increased use of the reward-optimal route, and the combined condition produced the largest effect. In control manipulations, randomly reassigning reward placement or lesioning either subthreshold connection prevented the network from taking the constructed route, and the effect reproduced across independently generated graphs. When we removed the externally injected fragments and generated replay solely from the network's own recurrent weights, the annealed schedule with reward-guided selection still potentiated the novel route. We next asked whether a route strengthened during replay could be selected and used during later waking behavior. Gating plasticity during both waking and replay with a signal equal to the rectified reward-prediction error (RPE) led the network not only to construct the novel route but also to adopt it during behavior, showing that already-learned routes produced no RPE and decayed, while only better-than-expected novel routes were selectively potentiated. These results show that a spiking network can use sleep replay to construct, and then exploit, a reward-optimal solution that no waking experience could generate. Our findings support the idea that sleep replay can do more than consolidate prior experience. Under the right plasticity and reward conditions, it can serve as a generative process for discovering new solutions.

Disclosures: R. Aalishah: None. **A. Hatami:** None. **I.E. Monosov:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.07/O6

Topic: B.05. Synaptic Plasticity

Support: NIH Grant DA044118
NIH Grant HD101642

Title: Microglial repopulation reverses impairments to hippocampal LTP after adolescent THC exposure

Authors: *C. M. GALL[1], J. CHAVEZ[1], A. A. LE[2], G. LYNCH[3];
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Abstract: Exposure to cannabinoids during adolescence can lead to long lasting impairments in cognitive function. We have shown that, in mice, treatment with tetrahydrocannabinol (THC), the principal psychoactive component in cannabis, during adolescence leads lasting impairment

in long term potentiation (LTP) in the lateral perforant path (LPP) in both males and females, and in the Schaffer-commissural (SC) projections to field CA1 in females only. In association with this, the acquisition of episodic memories which rely on the LPP was also impaired in THC treated animals. Other studies show that the same adolescent THC (ado-THC) treatment regimen leads to enduring disturbances in the homeostatic functions of microglia. Together these findings suggest the hypothesis that ado-THC treatment impairs microglial functions that support LTP. They suggest the further possibility that microglial repopulation in adulthood may restore synaptic plasticity and associated cognitive processes. To test for effects of repopulation on LPP LTP, male C57BL6 mice were given daily injections with THC (5 mg/kg, IP) or vehicle (Veh) from postnatal day (P) 30 to 43. Three weeks later the mice were placed on a diet containing the colony stimulating factor receptor 1 inhibitor PLX5622 (PLX, 1200ppm) for 8-10 days. We have determined that this PLX treatment causes more than 90% depletion of hippocampal microglia in C57BL6 mice as determined by quantification of IBA-1 immunoreactive cells (Chavez et al, 2025). The mice were then returned to normal diet and, after 4 to 8 weeks to allow for repopulation, the status of LPP-LTP was assessed using acute hippocampal slices. Analyses showed that LTP in the LPP to dentate gyrus (DG) projection was restored to normal control values with microglial repopulation in both Veh-PLX and THC-PLX groups. These results indicate that microglia are needed to support the unusual endocannabinoid-dependent form of LTP (Wang et al., 2016, 2018) expressed by the LPP to dentate gyrus system. In addition, they support the view that replacement of microglia, that carried the trace of early age insult, with newly differentiated copies can restore normal microglial functions.

Disclosures: C.M. Gall: None. **J. Chavez:** None. **A.A. Le:** None. **G. Lynch:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.08/O7

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R35 NS127219

Title: Input-Dependent Long-Term Potentiation in Hilar Mossy Cells of the Dentate Gyrus

Authors: C. DEL RIO DE AVILA, *M. B. JACKSON;
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Abstract: The dentate gyrus (DG) plays a critical role in memory encoding by supporting sparse granule cell recruitment and pattern separation. Hilar mossy cells (MCs) occupy a central position in this circuit by integrating and redistributing activity across multiple input pathways. We explored synaptic plasticity in MCs using voltage imaging with the hVOS probe in acute hippocampal slices combined with pathway-specific stimulation of distinct dentate gyrus inputs, including the molecular layer, granule cell layer (GCL), and CA3 region. LTP was induced using

theta-burst stimulation of each input. We found that LTP can be reliably induced in mossy cells following pathway-specific stimulation. Importantly, the magnitude of potentiation varied depending on the input pathway. Analysis of individual mossy cells further revealed variability in both baseline responses and the degree of potentiation following LTP induction within the same slice. This heterogeneity suggests that individual mossy cells may contribute differently to dentate gyrus function. Together, these findings indicate that plasticity in mossy cells is influenced by both pathway-specific input and cell-specific properties.

Disclosures: C. Del Rio De Avila: None. **M.B. Jackson:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.09/O8

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01HL142129
NIH Grant HL142129-04S1

Title: Dietary reversal and genetic deletion of Stat4 protect against hypercholesterolemia induced synaptic plasticity deficits

Authors: *C. M. HOLLANDER[1], X.-L. ZHANG[1], M. D'SILVA[2], J. NADLER[2], P. K. STANTON[1];
[1]Cell and Mol. Physiol., [2]Pharmacol., New York Med. Col., Valhalla, NY

Abstract: Dementia is characterized by progressive cognitive decline that disrupts daily life, with Alzheimer's disease accounting for 60-70% of cases. Aging stands as a primary risk factor, with hypercholesterolemia being a potential driving contributor. Frequently caused by a Western-style high-fat, high-cholesterol diet (HFD-C), hypercholesterolemia promotes vascular dysfunction, systemic inflammation, and blood-brain barrier disruption, which accelerates synaptic dysfunction. However, the inconsistent efficacy of cholesterol-lowering statins suggests that lipid reduction alone is insufficient for prevention. This discrepancy points toward hypercholesterolemia-induced systemic inflammation, with one candidate being the cytokine interleukin-12 (IL-12)/Stat4 signaling pathway, as a primary driver of synaptic failure. We evaluated how aging and HFD-C driven hypercholesterolemia impact long-term synaptic plasticity, and whether reducing Stat4 activation protects against resulting deficits. We assessed two forms of activity-dependent long-term synaptic plasticity, long-term potentiation (LTP) and depression (LTD), in 24- and 45-week low-density lipoprotein receptor knockout (Ldlr-/-) mice fed either chow or HFD-C diet from 8 weeks on. LTP showed no sex differences and was significantly impaired by chronic HFD-C feeding at 24 weeks. By 45 weeks, both dietary groups exhibited similar LTP magnitudes, smaller than 24-week chow-fed mice, yet larger than 24-week HFD-C fed mice. Remarkably, dietary reversal back to chow at 24 weeks successfully rescued

45-week LTP to levels comparable to 24-week chow-fed controls. Conversely, LTD exhibited sex-specific vulnerability. At 24 weeks, chronic HFD-C feeding had no significant effect on males but significantly increased LTD magnitude in females. By 45 weeks, males continued to show no changes in LTD. While females maintained similar LTD magnitudes on both diets, dietary reversal elicited a greater response than all other groups, but only achieved statistical significance with 24-week chow controls and 45-week HFD-C-fed mice. Finally, genetic deletion of Stat4 in myeloid cells provided robust neuroprotection, preserving LTP and LTD across both sexes at 24 and 45 weeks during HFD-C feeding. These results indicate reversal of diet at 24 weeks and Stat4 signaling as pivotal mechanistic links between HFD-C-induced inflammation and impaired synaptic plasticity. This suggests that targeting inflammatory signaling may be more clinically effective than lipid-lowering therapies alone at preventing the development of dementia.

Disclosures: C.M. Hollander: None. **X. Zhang:** None. **M. D'silva:** None. **J. Nadler:** None. **P.K. Stanton:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.10/P1

Topic: B.05. Synaptic Plasticity

Support: Research Grants Council of Hong Kong 11101922
Research Grants Council of Hong Kong 11101725

Title: A critical sound level for developing train ride noise-induced chronic depression

Authors: *Z. LIU[1], S. YANG[2];
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Abstract: Environmental noise has been linked to clinical depression in some epidemiological studies, but there is a lack of long-term animal models of noise-induced depression. This study exposed mice to simulated train ride noise for 60 days during juvenile to adolescent ages, which resulted in depression-like behaviors that persisted after a 30-day noise-free period into adulthood. Chronic noise exposure also altered the long-term synaptic plasticity (LTP) of the hippocampal dentate gyrus (DG)-DG network, via decreased sensitivity to metabotropic glutamate receptors (mGluRs) but not N-methyl-D-aspartate receptors. Attenuating the noise amplitude prevented depression-like behaviors as well as LTP impairment. Therefore, we provide a novel, stress-independent model for studying chronic depression in mice and highlight the significance of using ear protection and attenuating environmental noise for preventing affective disorders.

Disclosures: Z. Liu: None. **S. Yang:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.11/P2

Topic: B.05. Synaptic Plasticity

Support: 2R15DA049260

Title: LSD Restores Morphine-Eliminated Synaptic Plasticity in the Ventral Tegmental Area and Reversed Morphine-Induced Behavioral Preference

Authors: *C. BERRETT[1], M. VON GUNTEN[4], T. RUSSELL[1], S. HOFFMAN[2], J. EDWARDS[3];
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Abstract: Psychoplastogenic drugs are currently under heightened investigation as a treatment for neuropsychiatric disorders, including substance use disorders (SUDs). One working theory suggests that psychedelics counteract drug-induced maladaptive plasticity by 'resetting' synapses or creating new synapses. Here, we identify behavioral, physiological, and epigenetic impacts of lysergic acid diethylamide (LSD) on morphine-treated mice, focusing on the ventral tegmental area (VTA), an essential reward brain area. Male and female CD1 GAD67-GFP knock-in mice (P21-P65) received intraperitoneal (IP) morphine (10 mg/kg) injections every other day over eight days. Experimental mice received either a single hallucinogenic dose of LSD (0.3 mg/kg) following morphine treatments or received four LSD microdoses (0.03 mg/kg) administered with morphine injections. Accelerated extinction of morphine-induced conditioned place preference was noted for the hallucinogenic LSD treatment group ($n=10$, $p < 0.05$; ANOVA) and microdosed group ($n=9$, $p < 0.05$; ANOVA). Ex vivo whole-cell electrophysiology revealed that excitatory synaptic plasticity, which was eliminated in VTA GABA neurons following morphine exposure, was restored 24 hours after a single high dose of LSD ($n=7$ cells from $n=4$ mice, $p < 0.05$; ANOVA). However, low-dose LSD treatments did not restore long-term depression ($n=8$ cells from $n=5$ mice; $p> 0.05$; ANOVA). While behavior and plasticity do not need to correlate together, it is notable that LSD-induced changes are present in both experiments. In addition, positive control mice that received a hallucinogenic dose of LSD with no prior morphine treatments demonstrated a switch in plasticity of long-term depression to long-term depression that previously was unidentified ($n=8$ cells from $n=5$ mice; $p < 0.001$; ANOVA). To explore LSD's impact on potential epigenetic changes, whole-brain DNA methylation analysis in morphine-treated mice that received either saline or LSD post-morphine treatment revealed significant differential methylation profiles associated with LSD treatment in Zswim9, a zinc finger protein that is highly expressed in the brain during development. Our work not only identifies LSD as a possible therapeutic for SUD via its plastinogenic properties but also proposes an underlying mechanism by which LSD combats it. Collectively, these findings

suggest that LSD may reverse or prevent morphine-induced changes in reward circuit plasticity and attenuate measures of morphine preference.

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Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.12/P3

Topic: B.05. Synaptic Plasticity

Support: NIH T32 2T32MH014276-49
DoD Grant HT94252310458

Title: Effects of MDMA on cortical excitability and synaptic plasticity

Authors: *T. ANDERSON[1], A. P. KAYE[2];
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Abstract: MDMA-assisted therapy has shown durable efficacy for PTSD in Phase 3 clinical trials, but the cortical mechanisms by which acute MDMA produces persistent therapeutic effects remain poorly characterized. The medial prefrontal cortex (mPFC)contains dense expression of several subtypes of serotonin receptors on a variety of cell types, each with specific and unique effects on cellular physiology and circuit transmission. MDMA is a serotonin releasing agent and a psychoactive entactogen with profound effects on sensory information and cognitive function, modalities that modulate and recruit mPFC activity. To observe the effects of MDMA on cortical neuronal firing and potential synaptic plasticity, we combined in vivo single unit Neuropixels 2.0 recordings in mice receiving acute MDMA, slice whole-cell patch-clamp electrophysiology in mice 24 hours after MDMA, and longitudinal two-photon microscopy of dendritic spines. Analysis of the Allen Brain Cell (ABC) Atlas Consensus Whole Mouse Brain taxonomy, released in 2025, revealed cell type specific distribution of several serotonin receptors in the mPFC. Neuropixels recordings were performed in mice head fixed and walking on a treadmill 30 minutes before MDMA injection (baseline) and for the following 45 minutes after an i.p. injection of MDMA (7.8 mg/kg). Brain region specific analysis showed changes in excitability and firing rates in both fast-spiking and regular-spiking neurons in the mPFC and the adjacent regions compared to saline controls. Longitudinal two-photon microscopy showed mPFC spine density increased 24 hours after MDMA. Patch-clamp recordings of infralimbic cortex layer V pyramidal neurons 24 hours after MDMA injection revealed an increase in spontaneous excitatory post- synaptic current amplitudes compared to saline controls, with no change in event frequency, suggesting post-synaptic lasting potentiation induced by MDMA. Altogether, these findings showcase the acute and persistent effects of MDMA administration on

mPFC excitability and synaptic plasticity, identifying the mPFC as a candidate substrate underlying the acute psychoactive effects and lasting therapeutic effects of MDMA.

Disclosures: T. Anderson: None. **A.P. Kaye:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.13/P4

Topic: B.05. Synaptic Plasticity

Support: NINDS K99NS146613
Simons Foundation Junior Fellowship

Title: A Synaptic Basis for Cortical Reinforcement Learning using BMIs

Authors: *E. ALBARRAN[1], A. FUSHIKI[2], V. R. ATHALYE[2], D. S. PETERKA[1], R. M. COSTA[2];
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Abstract: Dopamine is a key neuromodulator of reinforcement learning, yet how it reshapes the synaptic landscape during learning remains unclear. We developed a closed-loop brain-machine interface (BMI) to selectively reinforce defined cortical neuronal ensembles in vivo while imaging synaptic activity. Using longitudinal two-photon calcium imaging of cortical dendrites and somata, combined with optogenetic stimulation of ventral tegmental area dopamine neurons, animals learned to volitionally activate reinforced ensembles. Reinforcement revealed a temporally precise credit-assignment window linking neural activity to dopamine release. Synapses active immediately before reinforced events preferentially potentiated, whereas uncorrelated inputs weakened. Structural imaging showed increased dendritic spine turnover and stabilization of newly formed spines, indicating ensemble-specific circuit rewiring. Regional dopamine receptor perturbations suggest frontal cortical reinforcement requires local dopamine signaling, while striatal dopamine is required for reinforcement across dorsal cortex. Together, these findings establish a synaptic framework for dopamine-driven cortical reinforcement learning and demonstrate how closed-loop BMI paradigms can causally link neuromodulation to circuit plasticity.

Disclosures: E. Albarran: None. **A. Fushiki:** None. **V.R. Athalye:** None. **D.S. Peterka:** None. **R.M. Costa:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.14/P5

Topic: B.05. Synaptic Plasticity

Support: 3R01NS116589-03S1
5R01NS116589-03

Title: Experimental and computational support for learned synaptic dynamics

Authors: *A. MARGOLIS, J. MCDOWELL, D. V. BUONOMANO;
UCLA, Los Angeles, CA

Abstract: Short-term synaptic plasticity (**STP**), in which synaptic efficacy changes in a use-dependent manner, endows synapses with rich dynamics. Although STP is ubiquitous across synapses in the mammalian brain, there is no consensus as to its computational function. Indeed, most neurocomputational models ignore STP, treating synaptic strength as a static property. While it has been shown that STP may interact with long-term plasticity, changes in synaptic dynamics have traditionally been viewed as an epiphenomenon of long-term potentiation or depression. Here, we propose that STP itself can be learned to enhance temporal computations. First, we experimentally test our Learned Synaptic Dynamics hypothesis, which proposes that STP is tuned in an experience-dependent manner to maximize synaptic efficacy at the time of concurrent pre- and post-synaptic activity. In effect, this hypothesis extends Hebbian plasticity into the temporal dimension. We chronically stimulated pre- and post-synaptic cells in cortical organotypic cultures using sparse dual-optogenetics, while varying the temporal relationship between pre- and postsynaptic stimulation. We found that 'Early'-trained synapses, in which post-synaptic activity occurred early in a train of presynaptic activity, generally exhibited short-term depression. In contrast, 'Late'-trained synapses, in which post-synaptic activity occurred late in a train of presynaptic activity, exhibited short-term facilitation or less short-term depression. We next developed a biologically plausible learning rule for learned synaptic dynamics. In this model, synapses do not have a single learnable parameter (weight) but rather four parameters that jointly govern baseline strength and synaptic dynamics. Our learning rule was able to reproduce the dynamics seen in 'Early' and 'Late'-trained synapses. In addition, we found that our learning rule was able to solve a variety of additional timing tasks: a counting task, in which synapses learned to maximize their efficacy at a specific ordinal pulse within a train, and an interval-selectivity task, in which synapses learned to preferentially respond to a specific inter-pulse interval. Together, our findings suggest that synapses are able to tune their short-term dynamics to enhance the processing of temporal information. Importantly, our results challenge the traditional view of synaptic strength as a static weight and suggest that tunable dynamic synapses can perform more sophisticated computations.

Disclosures: A. Margolis: None. **J. McDowell:** None. **D.V. Buonomano:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.15/P6

Topic: B.05. Synaptic Plasticity

Support: 5R01NS116589-03
3R01NS116589-03S1

Title: Synapses Learn to Tell Time

Authors: *J. MCDOWELL[1], A. MARGOLIS[1], D. V. BUONOMANO[2];
[2]Dept Neurobiol, [1]UCLA, Los Angeles, CA

Abstract: One of the most fundamental tenets in neuroscience is that information is stored in the strength of synapses and that learning relies on changes in synaptic strength. We aim to extend this tenet into the temporal domain by proposing that synapses not only learn to strengthen or weaken, but can also learn *when* to be weak or strong on the subsecond scale. **Short-term synaptic plasticity (STP)** is a form of presynaptic, use-dependent, plasticity in which consecutive spikes can elicit progressively weakening (short-term depression) or strengthening (short-term facilitation) postsynaptic potentials. Traditionally, STP has been viewed as a hardwired property of synapses that is primarily governed by initial release probability, leading to the standard view that strong synapses exhibit short-term depression and weak synapses exhibit short-term facilitation. Here, we propose the **Learned Synaptic Dynamics (LSD)** hypothesis, which predicts that the molecular mechanisms governing the direction, magnitude, and temporal profile of STP can be learned at the synaptic level to optimize the processing of temporal information. In its simplest form, LSD predicts that the presynaptic parameters governing STP undergo long-term changes that favor short-term depression when the early action potentials of a presynaptic train are paired with postsynaptic activity, and short-term facilitation when the late presynaptic spikes are paired with postsynaptic activity. Using a sparse, dual-opsin (ChR2 and Chrimson) approach in organotypic cultures, we provide the first experimental evidence that STP may be learned, and that learning is synapse-specific. By pairing postsynaptic (ChR2, 5 pulses, 50 Hz) activity to co-occur with the first or last spikes of a presynaptic train (Chrim, 12 pulses, 25 Hz), we shifted STP towards depression or facilitation, respectively. Further, within-slice controls indicate that this effect is only seen in $ChR2^{+}$cells that were directly stimulated during training, but absent in $opsin^{-}$ neurons. Next, we show that learned synaptic dynamics generalizes across different temporal intervals: by pairing the first or last of four presynaptic spikes (2 Hz) with a burst of postsynaptic activity, we were able to dramatically increase the percentage of trained cells exhibiting facilitation (0.2% and 54%, for first and last pairing, respectively). Finally, by quantifying STP dynamics, we demonstrated that LSD results from changes in the time constants of depression. Together, these results support the hypothesis that synaptic dynamics may be learned to optimize the processing of temporal information.

Disclosures: J. McDowell: None. **A. Margolis:** None. **D.V. Buonomano:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.16/Q1

Topic: B.05. Synaptic Plasticity

Support: MH118298
MH131717

Title: Spike-Timing-Dependent LTP Emerges through Probabilistic Silent Synapse Unsilencing

Authors: T. FU, *W. XU;
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Abstract: Synaptic strengthening at central synapses is inherently discrete and probabilistic, yet the mechanisms linking stochastic transmission (Katz, 1969) to long-term potentiation (LTP) remain incompletely understood. We developed a computational model in which each synaptic connection comprises multiple independent transmission sites, consistent with quantal analysis estimates of cortical release site number (Huang et al., 2010; Branco et al., 2009; Silver et al., 2003; Feldmeyer et al., 1999), each governed by a release probability and a binary silent or unsilenced postsynaptic state reflecting the absence or presence of AMPA receptors at individual sites. Presynaptic short-term plasticity dynamics are incorporated, reproducing paired-pulse facilitation across inter-stimulus intervals (Schoch et al., 2002) and presynaptic release site recovery (Schlüter et al., 2006) observed at central synapses. LTP emerges through NMDA receptor-dependent unsilencing of silent postsynaptic sites (Liao et al., 1995; Isaac et al., 1995) following coincident pre- and postsynaptic activity, governed by a spike-timing-dependent plasticity (STDP) rule with temporal dependence. Across multiple simulation runs, the model captures both the mean magnitude of potentiation and its substantial trial-to-trial variability across pairing delay and frequency domains (Bi and Poo, 1998; Sjöström et al., 2001), features classical models fail to reproduce. Parameter analysis identifies two necessary conditions: local cooperativity among adjacent transmission sites, required to produce spatially clustered potentiation, and repeated successful coincident pairings, required to stabilize newly unsilenced sites against reversal. Eliminating either condition disrupts experimentally observed potentiation distributions. These results establish silent synapse unsilencing as the postsynaptic mechanism by which stochastic release at individual sites accumulates into spike-timing-dependent LTP, providing a unified account of synaptic learning rules grounded in synapse-level dynamics.

Disclosures: T. Fu: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Pending. **W. Xu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Pending.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.17/Q2

Topic: B.05. Synaptic Plasticity

Title: Surface Mobility of Postsynaptic AMPARs Does Not Tune Synaptic Transmission

Authors: *K. S. KHOURY[1], T. SINGH[1], P. KURUP[1], J. Y. DELGADO[2];
[2]Biol., [1]Loyola Univ. Chicago, Chicago, IL

Abstract: AMPA-type glutamate receptors (AMPARs) mediate most fast excitatory synaptic charge transfer. Although short-term synaptic dynamics during repetitive stimulation are traditionally attributed to presynaptic mechanisms, previous studies proposed that lateral diffusion of AMPARs rapidly replenishes synaptic receptors after desensitization. Here, we revisit this model by restricting endogenous AMPAR surface mobility using cross-linking approaches. Consistent with prior work, AMPAR cross-linking significantly reduced paired-pulse ratio without significantly altering the coefficient of variation of evoked EPSC amplitudes, mEPSC amplitude, or mEPSC decay time. However, cross-linking also significantly reduced mEPSC frequency and the AMPA/NMDAR ratio, indicating a reduction in the number of functional AMPAR-containing synapses. Ongoing experiments will determine whether this reflects displacement of AMPARs from the postsynaptic density or bulk endocytosis of surface-expressed receptors. This data will be complemented by Monte Carlo simulations of AMPARs to test if these receptors move at rates sufficient to replenish desensitized receptors during fast synaptic transmission. Together, our findings support a model in which cross-linking displaces endogenous AMPARs from the synaptic surface, thereby reducing the number of functional synapses available to respond during repetitive stimulation. Under these conditions, changes in paired-pulse dynamics are better accounted for by a reduction in active synaptic responses rather than impaired receptor mobility. Because paired-pulse responses reflect both presynaptic release probability and the number of functional postsynaptic sites, loss of synaptic AMPARs can produce enhanced paired-pulse depression without requiring lateral diffusion to replenish desensitized receptors. These results suggest that prior interpretations of AMPAR cross-linking experiments may reflect a consequence of receptor loss rather than a physiological requirement for AMPAR surface mobility in tuning fast synaptic transmission.

Disclosures: K.S. Khoury: None. **T. Singh:** None. **P. Kurup:** None. **J.Y. Delgado:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.18/Q3

Topic: B.05. Synaptic Plasticity

Title: Development and Characterization of Conformation-Specific Antibodies Targeting Phosphorylated Threonine 19 in PSD-95

Authors: *J. ALVAREZ, P. KURUP, J. Y. DELGADO;
Biol., Loyola Univ. Chicago, Chicago, IL

Abstract: Activity-dependent synaptic plasticity is governed by posttranslational mechanisms that regulate the stability and molecular organization of postsynaptic protein complexes. Proline-directed phosphorylation of the N-terminus of PSD-95 promotes synaptic weakening during NMDAR-dependent LTD, yet this type of phosphorylation also alters the cis-trans isomerization of the adjacent peptidyl-prolyl bond. Despite its predicted importance, these conformational changes have not been directly measurable using existing molecular tools. In this presentation we describe the development of novel conformation-preferential antibodies that distinguish structural states of PSD-95 when Threonine 19 (T19), a site implicated in NMDAR-LTD, is phosphorylated. These antibodies were validated biochemically and in cellular assays, where signal increased following GSK3β-mediated phosphorylation and was lost upon dephosphorylation. These reagents represent the first conformation-preferential antibody-based tools capable of reporting phosphorylation-dependent conformational states of PSD-95 at T19. This strategy validates and expands prior framework for developing conformational-sensitive antibodies, an approach that can be applied to other synaptic proteins.

Disclosures: J. Alvarez: None. **P. Kurup:** None. **J.Y. Delgado:** None.

Poster

PSTR300: LTP and LTD: Pre- and Postsynaptic Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR300.19/Q4

Topic: B.05. Synaptic Plasticity

Title: Proline-directed phosphorylation and prolyl isomerization oppose each other to regulate PSD-95 ubiquitination and excitatory synaptic plasticity

Authors: *T. SINGH[1], P. KURUP[2], J. Y. DELGADO[2];
[2]Biol., [1]Loyola Univ. Chicago, Chicago, IL

Abstract: PSD-95 is a key scaffolding protein in excitatory synapses, playing a critical role in stabilizing synaptic receptors. Post-translational modifications such as phosphorylation and ubiquitination have been shown to regulate PSD-95's localization and stability. Threonine 19 (T19) phosphorylation has emerged as a key phosphorylation site involved in NMDAR-dependent LTD; however, its role in PSD-95 ubiquitination is unknown. This presentation aims to elucidate the role of T19 phosphorylation in regulating PSD-95 ubiquitination, and whether the peptidyl prolyl isomerase 1 (Pin1), a known phospho-T19 binding protein, modifies this process. Our results support the idea that T19 and S25 phosphorylation positively regulate PSD-95 ubiquitination. Furthermore, we found that the Pin1 binding to S25 lowered the

phosphorylation state of T19 and prevented PSD-95 ubiquitination. Finally, whole-cell recordings show that GSK3 overexpression depressed baseline synaptic transmission and partially blocked NMDAR-LTD, and both effects were rescued by Pin1 overexpression. Together, these findings provide insights into the molecular mechanisms regulating PSD-95 stability at synapses.

Disclosures: T. Singh: None. **P. Kurup:** None. **J.Y. Delgado:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.01/Q5

Topic: B.09. Glial Mechanisms

Title: Neuroinflammatory suppression of astrocytic BMAL1 defines a selective reactive astrocyte program

Authors: *X. MENG[1,2], X. ZHANG[1,2], J. KIM[1,2];
[1]Biomed. Sci., City Univ. of Hong Kong, Hong Kong, China; [2]Tung Biomed. Sci. Ctr., Hong Kong, China

Abstract: Astrocyte reactivity is a hallmark of neuroinflammatory diseases. Astrocytes contain functional circadian clocks that drive daily homeostatic rhythms, making them potential regulators of the transition from homeostatic to reactive states. However, it remains unclear whether neuroinflammatory conditions actively remodel endogenous astrocyte clocks and whether this helps define specific reactive astrocyte states. Previous studies, mainly based on genetic loss of the circadian transcription factor Bmal1, supported this idea but could not determine how neuroinflammatory conditions alter endogenous astrocyte clock function. Here, we combined in vivo and in vitro lipopolysaccharide (LPS)-based neuroinflammation models with circadian profiling, chromatin analysis, and bulk RNA-sequencing of purified microglia and astrocytes. In vivo and in vitro, neuroinflammation reorganized astrocyte clock output, with reduced amplitude and phase shifts of *Bmal1* and *Per1* rhythms, while reactive markers gained rhythmic expression. In vitro, these clock alterations occurred in astrocytes exposed to the inflammatory glial environment, but not after direct LPS treatment, indicating that paracrine glial signaling is the main driver. RNA-sequencing of microglia from the same neuroinflammatory glial cultures identified *Il1b* and *Tnf* as strong candidate mediators, and combined IL-1β/TNFα treatment was sufficient to suppress astrocyte clock genes and induce reactive marker expression. At the BMAL1 level, this clock suppression was accompanied by a modest reduction in BMAL1 protein but a marked decrease in BMAL1 occupancy at the *Per1* promoter, indicating a greater loss of transcriptional activity than protein abundance. To determine how reduced BMAL1 contributes to reactive remodeling, we compared astrocytes under neuroinflammatory conditions with astrocytes lacking *Bmal1* and found that reduced BMAL1 alone did not reproduce the full inflammatory response. Instead, it defined a selective subset of the reactive

astrocyte transcriptome marked most strongly by suppression of cell-cycle and chromosome-segregation pathways with limited innate immune activation. Together, these findings identify astrocytic BMAL1 as a key determinant of a distinct reactive astrocyte state under neuroinflammatory conditions and support the idea that reactive astrocyte heterogeneity is driven by multiple mechanisms rather than by a single master regulator.

Disclosures: X. Meng: None. **X. Zhang:** None. **J. Kim:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.02/Q6

Topic: B.09. Glial Mechanisms

Support: NSF GRFP
NIH Grant MH106460-06

Title: Microglia and Astrocyte Characterization in Clock delta19 mice

Authors: *J. GALLEGO[1], V. DHAWAN[2], S. NARAYANAN[1], C. PRESZLER[1], C. THOMPSON[2], D. SHI[2], T. CUI[3], C. A. MCCLUNG[4];
[2]Bioengineering, [3]Dept. of Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Psychiatry, Univ. of Pittsburgh Med. Sch., Pittsburgh, PA

Abstract: Microglia and astrocytes are critical regulators of neuroinflammation, and when functioning optimally, they coordinate repair, maintain synaptic homeostasis, and support neuronal survival. Both microglia and astrocytes are regulated by circadian rhythms, exhibiting rhythmic expression of inflammatory mediators and clock genes, such as Circadian Locomotor Output Cycles Kaput (Clock) gene. When the CLOCK gene is disrupted, as in the ClockΔ19 mutant mouse model, the mice display mania-like behavior, altered sleep patterns, and reduced anxiety. Although these behavioral changes have been well documented, little is known about glial cell activity within this mouse model. Previous work by Dr. Xinyan Tracy Cui's lab (University of Pittsburgh) revealed a significant difference in glial morphology in response to an injury, due to a microelectrode implant, within the ClockΔ19 mice. Specifically, endpoint immunohistology analysis showed a significant decrease in Iba-1 (microglia) and GFAP (astrocyte) intensities around the implantation site, contrary to the typical neuroinflammation response. The brains of Wild-Type mice (n = 6) and ClockΔ19 mice (n = 7) were extracted at ZT4 and ZT16, and immunohistochemistry for microglia and astrocytes was performed on the prefrontal cortex, dorsal striatum, and VTA. Preliminary morphological analysis suggests that more reactive astrocytes and fewer homeostatic microglia are present within the ClockΔ19 mice compared to the wild-type mice at ZT4. Additional studies at different time points and with other stressors are ongoing, as well as mania and depression focused behavioral analysis. This work

suggests that the CLOCK gene has a significant influence on glial cells during inflammatory processes, hinting at a possible target for stress and depression treatment.

Disclosures: J. Gallego: None. **V. Dhawan:** None. **S. Narayanan:** None. **C. Preszler:** None. **C. Thompson:** None. **D. Shi:** None. **T. Cui:** None. **C.A. McClung:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.03/R1

Topic: B.09. Glial Mechanisms

Support: NST Grant GTL24021-000
KIMST Grant RS-2025-02292973

Title: A 3D Astrocyte Microenvironment Model Enables Rapid Ca^{2+}-Resolved Analysis and Therapeutic Modulation of Oxidative Neuroinflammation

Authors: *Y.-J. KIM[1], D. WOO[2];
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Abstract: Astrocytes orchestrate key neuroinflammatory processes, yet conventional two dimentional (2D) cultures distort Ca^{2+}signaling and elevate inflammatory noise. Here, we introduce the Astrocytic Reactive-Calcium 3D microenvironment (ARC-3D), a tunable methacrylated gelatin (GelMA)-based 3D astrocyte microenvironment that enables stable long-term culture, improved transcriptional fidelity, and rapid Ca^{2+}-resolved functional assessment under perfusion. The optimized 3.5 wt% matrix supported quiescent, structurally mature astrocytes and markedly reduced the inflammatory baseline observed in 2D systems. Upon oxidative stimulation with H_2O_2, ARC-3D recapitulated hallmark features of reactive astrogliosis, including elevated basal Ca^{2+} levels, impaired receptor-evoked Ca^{2+} transients, induction of GFAP and MAO-B, and secretion of IL-6 and IL-1β, captured at second-to-minute timescales. Treatment with KDS12025, an H_2O_2-scavenging MAO-B modulator, partially restored Ca^{2+} homeostasis, suppressed Ca^{2+}-dependent cytokines, and selectively recovered gliogenic and metabolic signatures in transcriptomic analysis. In vivo intracerebroventricular H_2O_2 challenge validated the ARC-3D pathological trajectory and therapeutic modulation, highlighting strong in vitro-in vivo concordance. Collectively, ARC-3D offers a mechanistically precise, Ca^{2+}-resolved, and translationally aligned platform for decoding oxidative neuroinflammation and for advancing astrocyte-targeted therapeutic strategies.

Disclosures: Y. Kim: None. **D. Woo:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.04/R2

Topic: B.09. Glial Mechanisms

Support: US Department of Education GAANN Fellowship P200A240048

Title: Effect of cocaine and HIV-gp120 on astrocyte reactivity through the CCR5 receptor

Authors: *E. N. NEGRON-COLLADO[1], R. NOEL, Jr.[2];
[1]Biomed. Sci., Pontifical Catholic Univ. of Puerto Rico, Ponce, Puerto Rico; [2]Dept. of Basic Sci., Ponce Hlth. Sci. Univ., Ponce, PR

Abstract: HIV Associated Neurocognitive Disorders (HAND) remain prevalent despite effective treatment, particularly among individuals with comorbid substance use. Cocaine exposure exacerbates neuroinflammation and may potentiate HIV-mediated neuropathogenesis, which is critical in the development of HAND. Although astrocytes can have a neuroprotective role, it is possible that they contribute to HAND-associated neuroinflammation through the activation of the co-receptor CCR5 by HIV-gp120, a protein involved in viral entry and signaling. However, wether HIV-gp120 and cocaine use CCR5 as a mediator. However, whether CCR5 acts as a central mediator of astrocyte reactivity under combined exposure to cocaine and HIV-gp120 remains unclear. This study aims to demonstrate that cocaine potentiates astrocytes reactivity induced by HIV-gp120 via CCR5 signaling pathways, contributing to a proinflammatory environment associated with HAND neuropathogenesis. We will investigate the combined effects of cocaine and HIV-gp120 on astrocyte reactivity through CCR5-mediated mechanisms. Human astrocytoma cell lines (U87 CD4+ CCR5+) will be exposed to cocaine (1, 5, and 10 μM), gp120 (1.6 μg/mL), or their combination, in the presence or absence of the CCR5 pharmacological antagonist maraviroc. Astrocyte reactivity will be assessed by immunofluorescence targeting Vimentin, a cytoskeletal protein asssociated with reactive astrocytes. The MILLIPLEX Human Cytokine/Chemokine/Growth Factor Panel A will then be used to quantify proinflammatory cytokine secretion, including IL-6, IL-1β, and TNF-α . We expect that combined treatment with cocaine and HIV-gp120 will significantly increase Vimentin expression compared to single treatments, indicating amplified astrocyte reactivity. Elevated secretion of proinflammatory cytokines is also expected, and we anticipate these effects to be reduced by maraviroc, confirming CCR5-dependent mechanisms. This study will provide insight into the intersection of substance use and HIV neuropathogenesis, supporting CCR5 as a critical mediator of astrocyte driven neuroinflammation.

Disclosures: E.N. Negron-Collado: None. **R. Noel:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.05/R3

Topic: B.09. Glial Mechanisms

Support: R01DA057195-02S1

Title: Characterization of a novel astrocyte subtype in HIV-induced neuropathic pain

Authors: *A. DIBUA[1], S.-J. TANG[2];
[1]Stony Brook Univ., South Setauket, NY; [2]Anesthesiol., SUNY Stony Brook Univ., Stony Brook, NY

Abstract: An estimated 30-60% of people living with Human Immunodeficiency Virus 1 (HIV-1) experience chronic pain despite the use of antiretrovirals to suppress viral load. The HIV-1 envelope glycoprotein 120 (gp120) is known to promote neuroinflammation and disrupt neuronal circuitry in the spinal cord. One such mechanism by which this occurs is through the activation of reactive astrocytes. To further examine this contribution, we previously performed single nuclei RNA sequencing (snRNA-seq) of the spinal cord from an HIV-1 gp120 transgenic (Tg) mouse model and identified a novel astrocyte subtype characterized by its specific expression of Galectin 3 (Gal3), coined HIV pain-associated astrocyte (HIPA). Interestingly, we found that the ablation of Gal3 in the gp120Tg mice restored the spinal astrocyte population and pain behavior back to the wild-type phenotype. However, the process underlying HIPA development and the critical contribution to HIV pain pathogenesis remains unclear. Based on previous data, we hypothesize that HIPA originates from ependymal cells (tanycytes) in the central canal (CC) of the spinal cord. To evaluate this hypothesis, we generated a gp120/Nestin-GFP double transgenic mouse for lineage tracing experiments. We found GFP-labeled Gal3+ cells emerging from differentiating cells in the CC. We also observed in gp120Tg mice that Gal3+ cells express Vimentin, a marker of tanycytes. These findings suggest that HIPAs may originate from neural stem cell progenitors within the CC. To further test the idea, we sought to determine the effect of ablation of neural stem cells on HIPA genesis. We found that administration of temozolomide (TMZ), which targets proliferating cells including neural stem cells, diminished HIPA cells. To achieve greater specificity, we employed a Nestin-HSV-TK transgenic mouse model to enable temporally and spatially controlled ablation of proliferating neural progenitors through ganciclovir administration in a gp120Tg background. We use these integrative approaches to define the potential genesis of HIPAs from neural progenitors and/or astrogliosis. Results from the studies will advance our understanding of the pathogenic mechanisms underlying HIV-associated pain.

Disclosures: A. DiBua: None. **S. Tang:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.06/Web Only

Topic: B.09. Glial Mechanisms

Title: Cefepime and memantine synergistically reverse inflammation-induced chronic pain and depression by modulating astroglial glutamate transporter

Authors: *A. KHAN[1], P. J. RONAN[2], S. RAHMAN[1];
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Abstract: Chronic pain and depression remain a major health problem that affects millions of people worldwide, with effective treatment hindered by the complex neurobiological mechanisms involved in this comorbidity. Accumulating evidence suggests that inflammation-induced hyperglutamatergic neurotransmission, particularly through the N-methyl-D-aspartate receptor (NMDAR), within corticolimbic structures plays a central role in driving chronic pain and depressive symptoms. Therefore, targeting glutamate clearance via the astroglial glutamate transporter 1 (GLT-1) is critical for treating these comorbid conditions. We previously demonstrated that positive glutamate transporter modulator cefepime (CFP), a fourth-generation beta-lactam cephalosporin antibiotic reduces lipopolysaccharide (LPS)-induced chronic pain and depressive-like behaviors in mice by modulating hyperactive glutamatergic neurotransmission. In this study, we aimed to investigate the effects of CFP and memantine (MEM) on LPS-induced chronic pain, depression, anxiety, and cognitive deficit-like behaviors using behavioral paradigms. We also determined the effects of CFP and MEM on astroglial expression of GLT-1 in the hippocampus (HPC) and prefrontal cortex (PFC) using Western blot. Experiments were conducted in C57BL/6J male mice (7-9 weeks old). The chronic inflammatory response was induced by an intraperitoneal injection of LPS (0.75 mg/kg) for 7 consecutive days. CFP (50 mg/kg) and MEM (3 mg/kg) were administered intraperitoneally 1 h prior to LPS administration for 7 consecutive days. Two-way ANOVA revealed that combined treatment with CFP and MEM significantly increased the paw withdrawal threshold ($p < 0.0001$) and latency time ($p < 0.0001$) during the von Frey and hot plate tests, respectively. Combined administration of CFP and MEM significantly decreased immobility time in both the forced swim test ($p < 0.0001$) and the tail suspension test ($p < 0.0001$). Moreover, combined treatment with CFP and MEM showed a significant increase in open arm time during the elevated plus maze test ($p < 0.0001$) and spontaneous alternation between arms during the Y-maze test ($p < 0.0001$). Western blot analysis indicated that combined administration of CFP and MEM significantly reversed the downregulation of astroglial GLT-1 expression in the HPC ($p < 0.0001$) and PFC ($p < 0.0001$). Overall, these findings provide preclinical evidence that combined CFP and MEM treatment may offer a promising translational strategy for managing the frequently co-occurring conditions of chronic pain and depression.

Disclosures: A. Khan: None. **P.J. Ronan:** None. **S. Rahman:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.07/R4

Topic: B.09. Glial Mechanisms

Support: RS-2024-00402116
RS-2025-02215169
RS-2026-25475834

Title: Medial prefrontal astrocytes gate HPA axis activity and antidepressant efficacy through a cortico-hypothalamic stress circuit

Authors: *M. HWANG[1], D. RHEE[3], K. NOH[4], S.-Y. CHOI[5], S. LEE[2];
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Abstract: Chronic stress is a major risk factor for depression and is frequently accompanied by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Although reduced astrocyte density in the medial prefrontal cortex (mPFC) is a consistent feature of depression, whether prefrontal astrocytes actively regulate stress hormone output and antidepressant responsiveness remains unclear. Here, we tested whether mPFC astrocytes gate HPA axis activity through a cortico-hypothalamic stress circuit. In vivo fiber photometry revealed that mPFC astrocytes exhibited robust Ca2+ transients during acute stress-related events. Chemogenetic activation of mPFC astrocytes attenuated stress-induced corticosterone release and shifted circuit recruitment toward increased c-Fos expression in the anterior bed nucleus of the stria terminalis (aBNST) and reduced c-Fos expression in the paraventricular hypothalamic nucleus (PVH). Anatomical and functional analyses identified an mPFC-aBNST-PVH pathway through which prefrontal astrocytes constrain hypothalamic stress output. Chronic restraint stress and selective mPFC astrocyte depletion produced convergent endocrine, behavioral, and circuit phenotypes, including elevated corticosterone, depressive-like behavior, reduced excitatory drive in aBNST-projecting mPFC neurons and PVH-projecting aBNST neurons, diminished inhibitory input onto PVH neurons, and PVH hyperexcitability. Conversely, sustained activation of mPFC astrocytes during chronic stress preserved astrocyte density, maintained mPFC-aBNST-PVH circuit function, attenuated corticosterone elevation, and prevented depressive-like behavioral changes. Chronic fluoxetine treatment similarly preserved mPFC astrocyte density and normalized stress-regulatory circuit recruitment, whereas selective depletion of mPFC astrocytes abolished the behavioral and endocrine efficacy of fluoxetine under chronic stress. Together, these findings identify mPFC astrocytes as circuit-level gatekeepers of HPA axis homeostasis, stress vulnerability, and antidepressant responsiveness through regulation of an mPFC-aBNST-PVH pathway.

Disclosures: M. Hwang: None. **D. Rhee:** None. **K. Noh:** None. **S. Choi:** None. **S. Lee:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.08/R5

Topic: B.09. Glial Mechanisms

Support: NSF OIA-2242771
Veterans Affairs BX005403
NIH R21 AA030086

Title: Microglial Remodeling of Astrocyte-Synapse Interactions Following Adolescent Ethanol Exposure

Authors: *O. COULTER[1,2], Q. OWENS[1,2], L. STANLEY[1,2], J. SEAGRAVES[1,2], S. TYSOR[1,2], H. G. SEXTON[1,2], M.-L. RISHER[1,2];
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Abstract: Adolescence is a crucial period of neurological development. Binge-drinking during this period has been associated with long-term disruption of neuronal and cognitive function. How non-neuronal cells contribute to these deficits remains understudied despite growing evidence that astrocytes are important regulators of neuronal function. A key structure that is affected by adolescent intermittent ethanol (AIE) exposure is the tripartite synapse, which is comprised of a pre- and post-synaptic terminal that are ensheathed by a peripheral astrocyte process (PAP). This ensheathment is critical for the regulation of synaptic activity and neuronal health. Our previous data demonstrate that AIE disrupts the proximity of PAPs and synapses in the male hippocampus. Here we begin to investigate how and why PAP-synaptic proximity is compromised following AIE in the dorsal hippocampus. To address this question, male and female rats received AIE followed by a 26-day abstinence period. Using a combination of adeno-associated viruses (AAV), immunohistochemistry (IHC), and confocal microscopy, we generated 3D astrocyte and microglial reconstructions using IMARIS. Astrocyte reconstruction was used to assess changes in terminal branch complexity indicative of microglial phagocytosis of PAPs and/or astrocyte remodeling. Microglial reconstruction and quantification of astrocyte membrane internalization were conducted to determine whether microglia engulf astrocyte processes. Bridging protein expression and interactions were quantified to rule out impairments in protein-protein interactions. Results show a reduction in PAP number without an overall reduction in branch number. Additionally, AIE increased astrocyte engulfment by microglia. Ongoing analyses of branch complexity and bridge protein interactions will also be presented. We predict that AIE drives microglial phagocytosis of astrocyte PAPs in adulthood. Understanding the mechanisms underlying tripartite synapse decoupling may reveal how AIE produces persistent cognitive dysfunction into adulthood.

Disclosures: O. Coulter: None. **Q. Owens:** None. **L. Stanley:** None. **J. Seagraves:** None. **S. Tysor:** None. **H.G. Sexton:** None. **M. Risher:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.09/R6

Topic: B.09. Glial Mechanisms

Support: NSF OIA-2242771
NIH R21AA030086
Veterans Affairs BX005403

Title: Sex Dependent Changes of Astrocyte-Synaptic Remodeling and Behavioral Function by Rosiglitazone Following Adolescent Binge Ethanol Exposure

Authors: K. CRANK[1], D. SANGANI[2,3], T. MUCK[2,3], O. COULTER[2,3], H. G. SEXTON[2,3], M. JONES[2,3], ***A. IHLENFELD**[2,3], G. ANGELONA[2,3], M.-L. RISHER[2,3];
[1]Biomed. Sci., [2]Marshall Univ., Huntington, WV; [3]Hershel 'Woody' Williams Veterans Affairs Med. Ctr., Huntington, WV

Abstract: Excessive binge drinking often begins during adolescence and peaks in early adulthood, a critical period of on-going brain maturation. Human studies show that adolescent binge drinking can result in long-term behavioral dysregulation and increased risk of developing an alcohol-use disorder in adulthood. Using the adolescent intermittent ethanol (AIE) model, we previously demonstrated maladaptive changes in the contextual fear conditioning task that were associated with dorsal hippocampal (dHipp) astrocyte reactivity, aberrant astrocyte signaling, tripartite structural remodeling, and astrocyte and neuronal oxidative stress. Additionally, we observed that rosiglitazone (ROSI), a drug used for Type-II diabetes, may be an effective therapeutic capable of reducing neuron- and astrocyte-associated oxidative stress. We hypothesize that ROSI administration is sufficient to rescue AIE-induced oxidative stress, tripartite structural remodeling, and cognitive deficits in adulthood. On PND 24, male and female Sprague-Dawley rats underwent AIE or H_2O (i.g.). Animals then received ROSI or Vehicle (i.g.) for 20 days. In adulthood, animals underwent behavioral testing or were euthanized for tissue collection. Brain tissue was used for immunohistochemistry (IHC), stimulated depletion emission microscopy (STED), or confocal microscopy and was analyzed using Synbot to evaluate tripartite colocalization and oxidative stress marker expression. Following AIE, we observed a sex-dependent increase in peripheral astrocyte process (PAP) proximity to inhibitory synapses and loss of proximity at excitatory synapses in the dHipp, both of which were rescued by ROSI administration. ROSI administration resulted in a reduction in astrocyte-specific lipid accumulation, indicative of improved oxidative stress outcomes in the AIE and control groups only in females. In contrast, males displayed an increase in oxidative stress markers in the AIE+ROSI group. Astrocyte branch morphology and behavioral results will also be shown. These results indicate that ROSI administration influences the long-term effects of AIE in a sex-specific manner. Future studies will investigate the region-specific effects of ROSI in the prefrontal cortex and amygdala and further investigate how ROSI influences oxidative stress signaling and synaptic function following AIE in adulthood.

Disclosures: K. Crank: None. **D. Sangani:** None. **T. Muck:** None. **O. Coulter:** None. **H.G. Sexton:** None. **M. Jones:** None. **A. Ihlenfeld:** None. **G. Angelona:** None. **M. Risher:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.10/S1

Topic: B.09. Glial Mechanisms

Support: NIAAA U01AA020912
R01AA027231
U01AA013498
P60AA006420
T32 AA007456

Title: Astrocyte-expressed STAT3 regulates glutamate homeostasis and binge ethanol drinking in mice

Authors: *M. GALÁN-LLARIO[1], H. CHEN[2], C. M. ERIKSON[3], R. VLKOLINSKY[4], M. BAJO[5], M. ROBERTO[6], A. W. LASEK[7];
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Abstract: STAT3 is a transcription factor activated by cytokine and growth factor signaling that promotes astrocyte reactivity and neuroinflammation. STAT3 has also been shown to regulate the expression of astrocyte-enriched glutamate transporters. To determine whether astrocyte-expressed STAT3 regulates glutamate transporter expression and glutamate homeostasis *in vivo*, we created conditional astrocyte *Stat3* knockout mice (Stat3aKO) by crossing Aldh1l1-CreERT2 to Stat3^{flox} mice. Mice (Cre-, controls; Cre+, Stat3 aKO) were treated with tamoxifen at 7 weeks old to knockout *Stat3* in adult astrocytes. At least 3 weeks after tamoxifen treatment, we measured transcript levels of *Slc1a2*, *Slc1a3*, *Slc7a11*, and *Slc17a8* (n=15-10 group/sex/genotype) in the medial prefrontal cortex (PFC) by quantitative real-time PCR. *Slc1a2* and *Slc17a8* were significantly decreased in Stat3 aKO (two-way ANOVA, genotype effect, $p<0.05$). *In silico* analysis identified predicted STAT3 binding sites within the *Slc1a2* promoter region, supporting direct transcriptional regulation. We also found decreased SLC1A2 (GLT-1) protein in the PFC of male Stat3 aKO compared to controls by western blot. These results suggested that glutamate uptake might be impaired in male Stat3 aKO. We recorded spontaneous excitatory post-synaptic currents (sEPSCs) in male Stat3 aKO and control prelimbic pyramidal neurons (Cre -, n= 25 cells from 4 mice and Cre +, n = 28 cells from 4 mice) and found a significant increase in mean sEPSC amplitude, but not frequency (unpaired t-test, $p<0.05$),

suggesting enhanced postsynaptic glutamatergic receptor function. To determine if there were behavioral phenotypes in Stat3 aKO, we tested mice for open-field locomotor activity and anxiety-like behavior using the light-dark box. Stat3 aKO did not differ from controls in these tests. We previously demonstrated that mice treated systemically with a STAT3 inhibitor consume less ethanol. To determine if Stat3 aKO have an ethanol consumption phenotype, we tested them for binge ethanol consumption using the drinking in the dark test over 12 sessions. Male (n=10 Cre - and 9 Cre +), but not female (n=8 Cre - and 11 Cre +), Stat3aKO consumed significantly less ethanol than controls (two-way RM ANOVA, genotype effect in males, $^{**}p=0.0041$). These results indicate impaired astrocytic glutamate clearance in male Stat3aKO mice and suggest that STAT3 is a regulator of binge drinking, possibly through glutamate transporter expression. This study implicates neuroimmune astrocyte signaling to cortical excitatory neurotransmission and ethanol consumption.

Disclosures: M. Galán-Llario: None. **H. Chen:** None. **C.M. Erikson:** None. **R. Vlkolinsky:** None. **M. Bajo:** None. **M. Roberto:** None. **A.W. Lasek:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.11/S2

Topic: B.09. Glial Mechanisms

Support: NIDA

Title: Astrocytic sex-specific heterogeneity in response to cocaine

Authors: B. P. NABIT[1], T. MARKOVIC[2], G. TAN[2], V. KONDEV[2], A. LABANCA[3], E. J. NESTLER[2], ***L. HOLT**[1,2];
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Abstract: Drug addiction is characterized by neurobiological adaptations that support a shift from goal-directed behaviors to habitual, compulsive drug-seeking with persistent effects on cognition and decision-making. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, evidence increasingly indicates that astrocytes also exhibit cellular, molecular, and transcriptional plasticity and contribute to aspects of drug addiction. We previously utilized whole cell sorting of nucleus accumbens (NAc) astrocytes and RNA-sequencing (RNA-seq) to demonstrate that the astrocyte transcriptome responds robustly to cocaine self-administration and implicated, for the first time, transcription factor CREB as a cocaine-induced transcriptional regulator in astrocytes. Subsequent experiments identified astrocytic CREB modulates the

rewarding and reinforcing properties of cocaine through modulation of astrocytic calcium dynamics and regulation of D1-medium spiny neuronal activity. These effects were sex-specific, with neither cocaine-induced CREB activation in female astrocytes nor an effect on the rewarding properties of cocaine with viral-mediated female astrocytic CREB manipulation. Reminiscent of neuronal CREB-mediated ensembles, new preliminary data indicate that not every astrocyte activates CREB following exposure to cocaine. Current work is focused on identifying if astrocytic CREB activity defines transcriptionally distinct astrocyte subtypes and their associated gene regulatory networks. To address these questions, we performed single nucleus RNA-seq (snRNA-seq) from the NAc in male and female mice following cocaine intravenous self-administration. Preliminary analysis identifies sex-specific gene regulation across three astrocyte subclusters, with more differentially expressed genes in females compared to males. Furthermore, while female astrocytes displayed a balanced proportion of up- and downregulated DEGs, male DEGs were predominantly downregulated (>90%). Current future directions include further data analysis to investigate the sex-specific astrocytic response, including pathway analysis, cell-cell signaling communication patterns, and activated gene regulatory networks.

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Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.12/S3

Topic: B.09. Glial Mechanisms

Support: NIH T32 DA050558-03
1R21MH136486 - 01A1
Estée Lauder Epigenetics Fellowship

Title: Dopaminergic Astrocyte-Neuron Crosstalk in the Ventral Tegmental Area

Authors: *L. OTSUKA[1], S. B. OSTLUND[2], E. BORRELLI[1];
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Abstract: Nearly 1 in every 7 people worldwide live with a mental disorder. Chronic alterations in dopamine (DA), a primary neuromodulator in the brain, have largely been implicated in numerous mental health conditions due to the critical roles DA signaling plays in regulating cognition, reward, and motor control. This wide variety of functional and behavioral control by DA is fundamentally attributed to its neuroanatomical signaling pathways. DA neurons primarily originate in the ventral midbrain, namely in the ventral tegmental area (VTA) and substantia nigra (SN), but project to transmit DA to a vast number of target regions throughout the brain.

Importantly, while downstream responses to altered DAergic transmission in regions receiving DA input have been widely studied, local signaling and circuitry within the VTA remain largely uncharacterized. Moreover, newly emerging research has identified the expression of dopamine D2 receptors (D2Rs) on not only pre- and post-synaptic neurons, but also on astrocyte perisynaptic processes. Given the well-established roles for astrocytes in regulating processes known to be disrupted in psychiatric disorders, including neurotransmitter homeostasis and neuroinflammatory coordination, the mechanisms linking local VTA DA signaling and astrocyte function must be clarified. Here, we utilize three distinct transgenic mouse models in which D2R has been selectively ablated from all ventral midbrain cells (DA-D2RKO), only VTA neurons (hSYN-D2RKO), or only VTA astrocytes (GFAP-D2RKO) in order to elucidate how this local signaling and circuitry contribute to downstream behavioral functions under both basal conditions and in response to dysregulation of DA signaling through chronic methamphetamine (MA) administration. Assessment of motor sensitization to MA revealed a striking inhibition in DA-D2RKO mice compared to their wild type (WT) littermates - a phenotype recapitulated in hSYN-D2RKO but not GFAP-D2RKO mice. In-vivo imaging of the VTA following MA administration highlights an aberrant DA-GABA ratio in DA-D2RKO mice, further clarified in GFAP-D2RKO mice as astrocyte-regulated mechanism of inhibitory control. Finally, molecular analyses indicate upregulated inflammatory synaptic pruning in the absence of DAergic control over VTA astrocytes. Taken together, we provide evidence of a coordinated quadripartite synaptic circuitry in the VTA that both responds to and mediates the function of DA release throughout the brain.

Disclosures: L. Otsuka: None. **S.B. Ostlund:** None. **E. Borrelli:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: B.09. Glial Mechanisms

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West Virginia IDeA Network of Biomedical Research Excellence Grant P20GM103434
COBRE ACCORD Grant 1P20GM121299
West Virginia Clinical and Translational Science Institute Grant 2U54GM104942

Title: Early Life Neurotoxic Insult Disrupts Astrocyte Metabolism and Tripartite Synapse Maturation in the Developing Prefrontal Cortex

Authors: *F. O. MALONE[1], A. Q. NATO, Jr.[2], S. AKTER[2], W. C. RISHER[2];
[1]Marshall Univ., Huntington, WV; [2]Biomed. Sci., JC Edwards-Marshall Univ. Sch. of Med., Huntington, WV

Abstract: At the tripartite synapse, peripheral astrocyte processes (PAPs) interact closely with neurons to influence synaptic maturation and function. Emerging evidence supports that dysfunction of these neuron-astrocyte interactions contributes to psychiatric and neurological complications; however, the long-term consequences of tripartite synapse dysregulation during early-life development are largely unknown. One neurotoxic insult increasingly relevant to early-life brain development is prenatal opioid exposure (POE), which is associated with behavioral and cognitive consequences in humans. While much is known regarding the behavioral effects of POE, the molecular mechanisms by which POE alters CNS function remain poorly understood. Molecular and cellular changes associated with POE were investigated within the adolescent prefrontal cortex (PFC), a critical region for reward and executive function. scRNA-seq of astrocyte-enriched P10 cortical cell mixtures revealed approximately 600 differentially expressed genes (DEGs) with POE compared to vehicle treatments. Genes associated with astrocyte structure and homeostasis were downregulated, while genes associated with mitochondrial function and lipid metabolism were upregulated. Preliminary spatial transcriptomics (Visium HD) within the PFC further corroborates these findings, in addition to identifying subregion-specific vulnerabilities. These results suggest that the synaptic deficits associated with POE may be driven by disruption of astrocyte maturation and bioenergetics. Human astrocytes were used to test whether lipid metabolism pathways contribute to opioid-induced astrocyte stress. Cells were treated acutely with buprenorphine in the presence or absence of fatty acid binding protein (FABP) inhibitors and DHA lipid loading. Following treatment, fluorescence immunocytochemistry (ICC) for 8-oxoG (oxidative nucleic acid damage), TOM20 (mitochondrial outer membrane marker), and perilipin-2 (lipid droplet-associated protein) confirmed FABP-dependent oxidative stress, mitochondrial disruption, and exacerbated lipid accumulation following opioid exposure in a translationally relevant *in vitro* model. The relevance of these metabolic stress observations is currently being validated *in vivo* using a mouse model of POE that we have previously used to confirm long-term changes in excitatory and inhibitory synaptic connectivity in the PFC. Taken together, our work has revealed a crucial role for astrocyte metabolism in the persistent disruption of tripartite synaptic connectivity and function following early life opioid exposure.

Disclosures: F.O. Malone: None. **A.Q. Nato:** None. **S. Akter:** None. **W.C. Risher:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.14/S5

Topic: B.09. Glial Mechanisms

Support: NIH Grant

Title: Prenatal THC Disrupts Astrocytic Mitochondrial Function in a Sex- and Region-Specific Manner

Authors: *V. SYROPOULOU[1], N. HARRIS[2,3], P. WILSON[2,4], T. FRACHISEUR[2,5], M. GRAMLICH[2,4], M. N. REED[6];
[1]Drug DIscovery and Develop., [3]Biol. Sci., [4]Physics, [5]Biomed. Sci., [6]Drug Discovery & Develop., [2]Auburn Univ., Auburn, AL

Abstract: Cannabis use during pregnancy is increasing, yet the cellular mechanisms underlying sex-biased neurodevelopmental consequences remain poorly understood. Astrocytes play critical roles in hippocampal circuit maturation through glutamate handling and metabolic support of neurons, both of which are energetically dependent on mitochondrial function. We hypothesized that prenatal THC exposure disrupts astrocytic mitochondrial homeostasis in a sex- and region-specific manner during early postnatal development, with downstream consequences for glutamate transporter expression. Primary hippocampal and cortical astrocytes were isolated from male and female rat pups (P2-3) born to dams exposed to THC or vehicle throughout gestation. Mitochondrial membrane potential was assessed by JC-1 ratiometric imaging, mitochondrial morphology by MitoView fluorescence microscopy with automated particle analysis, and functional respiratory parameters by high-resolution respirometry. Western blot analysis of glutamate transporters and mitochondrial dynamics proteins is ongoing. Preliminary data reveal that prenatal THC exposure significantly reduces mitochondrial membrane potential across astrocyte populations, with sexually dimorphic directionality in hippocampal astrocytes. Strikingly, female hippocampal astrocytes exhibit comprehensive mitochondrial fragmentation, as evidenced by reduced aspect ratio, increased circularity and elevated percentage of fragmented mitochondria, while male hippocampal astrocytes show no structural remodeling despite functional membrane potential changes. Cortical astrocytes show depolarization without morphological reorganization at equivalent developmental stages. These findings identify female hippocampal astrocytes as uniquely vulnerable to prenatal THC-induced mitochondrial structural remodeling, suggesting a novel astrocyte-specific mechanism that may contribute to the sex-biased hippocampal vulnerability observed in adolescent offspring of cannabis-exposed dams.

Disclosures: V. Syropoulou: None. **N. Harris:** None. **P. Wilson:** None. **T. Frachiseur:** None. **M. Gramlich:** None. **M.N. Reed:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.15/S6

Topic: B.09. Glial Mechanisms

Support: NSTC-114 -2927-I-182A-501 -
NSTC-115 -2927-I-182A-501 -

Title: Maternal High-Fructose Diet Programs Hypothalamic Mitochondrial Dysfunction and Synaptic Vulnerability in Female Offspring: Mitigation by tBHQ via Nrf2 Signaling

Authors: *C.-W. J. WU[1,2], K. L.-H. WU[3];
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Abstract: Maternal nutrition fundamentally shapes offspring brain metabolism and subsequent susceptibility to neurological disorders. Although excessive gestational and lactational fructose intake is known to induce hypothalamic metabolic dysregulation, the underlying mitochondrial mechanisms remain poorly understood. This study investigated female Sprague-Dawley offspring from dams fed either a normal diet (ND) or a high-fructose diet (HFrD) during gestation and lactation, evaluated at 1 and 3 months of age. Maternal HFrD provoked an age-dependent suppression of hypothalamic electron transport chain activity, accompanied by elevated oxidative protein modifications, a shift toward mitochondrial fission/fragmentation, and blunted induction of fusion markers. By 3 months of age, adaptive upregulation of PGC-1α and TFAM emerged alongside a pronounced reduction in key synaptic proteins, including synaptophysin, PSD95, and Tau, indicating that cumulative mitochondrial and redox stress precipitates molecular synaptic vulnerability. Furthermore, in the paraventricular nucleus, Nrf2 immunoreactivity within NeuN-positive neurons exhibited a distinctive perinuclear punctate pattern that was depleted by maternal HFrD but restored via therapeutic intervention. Remarkably, a 2-week course of the electrophilic antioxidant tert-butylhydroquinone (tBHQ) prior to the 3-month endpoint successfully mitigated oxidative damage, augmented Nrf2-associated antioxidant signaling, and normalized synaptic protein expression. Collectively, these findings identify an age-gated hypothalamic mitochondrial-redox phenotype linking maternal fructose exposure to molecular synaptic vulnerability in female offspring, highlighting Nrf2-mediated redox signaling as a promising, modifiable target to counteract maternal diet-induced neuro-metabolic programming.

Disclosures: C.J. Wu: None. **K.L. Wu:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.16/S7

Topic: B.09. Glial Mechanisms

Support: Grant No. T32GM152796

Title: Determining the Role of Astrocytic Nf1 Mutation in Driving Ras-dependent Neurological Deficits in Neurofibromatosis Type 1 (NF1)

Authors: *A. ECHEANDÍA[1], Y. PAN[2];
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Abstract: Neurofibromatosis Type 1 (NF1) is a genetic disorder affecting ~1 in 3,000 individuals and is best known as a tumor-predisposition syndrome. All patients carry a monoallelic NF1 mutation, and tumor formation or other complications can occur when a second somatic "hit" causes biallelic loss. The *NF1* gene encodes neurofibromin, a Ras-GTPase activating protein that accelerates conversion of Ras-GTP to Ras-GDP. Loss of neurofibromin leads to Ras hyperactivation and increased downstream MAPK/ERK and PI3K/AKT signaling. NF1 patients exhibit features such as café-au-lait macules, neurofibromas, and optic pathway gliomas; however, up to 75% experience neurological or cognitive impairments, including learning deficits, attention-related issues, and motor dysfunction. These symptoms overlap with other Ras/MAPK-related disorders (RASopathies), including Noonan and Costello syndromes, all of which display neurobehavioral phenotypes. Early studies in global *Nf1*-mutant mice demonstrated learning and motor impairments driven by Ras hyperactivation, and pharmacologic Ras inhibition rescued these deficits. While neuron, oligodendrocyte, and microglia-specific *Nf1* models have provided insight into cell-type specific contributions to behavior, the role of astrocytes remains poorly defined. Astrocytes regulate CNS homeostasis, including neurotransmitter uptake, ion balance, BBB support, and synaptic development and refinement. Recent work shows that Ras-MAPK pathway mutations disrupt astrocyte function and can impair cognition, suggesting astrocytes may play a critical role in *Nf1*-associated neurological deficits. To address this gap, we generated an astrocyte-specific *Nf1*-mutant mouse model to determine how *Nf1* loss alters astrocyte signaling and contributes to behavioral dysfunction. We will isolate astrocytes to examine Ras pathway hyperactivation and transcriptional changes, and assess cognition and motor behavior in vivo using the Puzzle Box, Open Field, Novel Object Place Recognition, and Beam Walk tests. Preliminary results indicate emerging behavioral deficits in astrocyte-specific *Nf1* mutants. This work will clarify astrocyte-specific mechanisms underlying NF1 and may reveal new therapeutic targets for NF1-associated neurobehavioral symptoms.

Disclosures: A. Echeandía: None. **Y. Pan:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.17/S8

Topic: B.09. Glial Mechanisms

Support: NIH Grant DP2NS136873
NIH Grant T32NS007431

Title: Uncovering the role of astrocytic hepaCAM in neural circuit stability and neurodevelopmental epilepsy

Authors: *B. DOGAN[1,2], K. BALDWIN[3];
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Abstract: Synaptic dysfunction is a shared hallmark of many neurodevelopmental disorders. In epilepsy, this dysfunction drives abnormal excitatory and inhibitory neurotransmission and seizure generation. Astrocytes, a major glial cell type, interact closely with synapses via cell adhesion molecules to regulate synapse formation and function. An emerging theme among studies investigating astrocyte-synapse interactions is that astrocytes play critical roles in balancing synaptic excitation and inhibition, however, the mechanisms underlying this regulation remain unclear. Our lab previously identified the astrocyte-enriched transmembrane protein hepatic and glial cell adhesion molecule (hepaCAM) as a novel regulator of synaptic organization and function. We observed hepaCAM expression at both excitatory and inhibitory synapses via super resolution microscopy and found that conditional deletion of *Hepacam* from astrocytes during brain development significantly increased excitatory synaptic strength and significantly decreased inhibitory strength, an alteration at the synapse consistent with circuit imbalance. In humans, mutations in *HEPACAM* cause megalencephalic leukoencephalopathy with subcortical cysts (MLC), an infantile onset leukodystrophy characterized by macrocephaly, epilepsy, and intellectual deficits. These findings further suggest an important role for astrocytic hepaCAM in maintaining neural circuit stability, yet the molecular function of hepaCAM at the synapse remains unknown. To address this knowledge gap, I performed unbiased quantitative proteomics of post synaptic density (PSD) fractions isolated from the cortex of juvenile astrocyte-specific *Hepacam* conditional knockout (cKO) mice and littermate controls. Bioinformatic analysis revealed significant reductions in proteins critical for synapse organization, signal transduction, vesicle-mediated transport, and cellular localization in *Hepacam* cKO PSD fractions, implicating astrocytic hepaCAM in the regulation of synaptic protein organization and stability. Ongoing studies are leveraging super-resolution microscopy to elucidate how astrocytic hepaCAM organizes excitatory and inhibitory synaptic components, as well as *in vivo* seizure modeling to assess how hepaCAM loss during critical developmental windows impacts seizure susceptibility. Together, this work reveals the molecular pathways by which an astrocyte-specific cell adhesion molecule regulates synaptic activity and neural circuit stability, highlighting potential therapeutic targets and providing new insight into glial contributions to neurodevelopmental epilepsy.

Disclosures: B. Dogan: None. **K. Baldwin:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.18/T1

Topic: B.09. Glial Mechanisms

Support: IZLCZ0_206045
IZLIZ3_200297
310030_192463
3200-0-239999
Synapsis Foundation No. 2020-PI02

Title: The role of astrocytes in rat behaviors associated with autism spectrum disorders

Authors: *N. VERDA[1], E. VAN DEN BURG[1], S. CHATTARJI[2], R. STOOP[1];
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Abstract: Autism Spectrum Disorders (ASD) are neurodevelopmental conditions characterized by altered social behavior, anxiety-related phenotypes, and neuronal hyperexcitability. Astrocytes are increasingly recognized as active regulators of synaptic transmission, extracellular homeostasis, and circuit excitability, and may therefore contribute to the excitation/inhibition imbalance observed in ASD. As Fragile X Syndrome (FXS), the most common monogenic cause of ASD, has been linked to astrocyte-driven neuronal dysfunction in human iPSC models (Sharma et al., 2023, Cell Reports), we hypothesize that astrocytic Ca^{2+} signaling in the medial prefrontal cortex (mPFC) contributes to ASD-relevant behavioral phenotypes. To first assess astrocytic Ca^{2+} activity and establish our ability to monitor it, we injected adeno-associated viral (AAV) vectors expressing the calcium indicator GCaMP6f under the GFAP promoter into the mPFC of 8-10-week-old female wild-type rats. In initial experiments, we confirmed astrocyte-specific GCaMP expression by immunohistochemistry using GFAP antibodies and demonstrated changes in intracellular calcium in response to high-potassium stimulation. We then used AAV vectors to express mCherry and iBARK, an inhibitory peptide known to reduce Gq GPCR-mediated calcium release from intracellular stores (Nagai et al., 2021, Neuron), in mPFC astrocytes. We used immunohistochemical analyses with GFAP and S100β antibodies to evaluate their colocalization with mCherry. We then assessed anxiety-like behavior, sociability, and social buffering of fear, a paradigm in which the presence of a conspecific reduces conditioned fear responses during retrieval (Hegoburu C., Tang Y., Niu R. et al., 2024, Nat. Comm.). While iBARK showed no effect on anxiety-like behavior in the elevated plus maze or social preference and social novelty tests, it reduced social buffering of fear during fear retrieval, suggesting that astrocytic Ca^{2+} signalling within the mPFC is selectively engaged in socially mediated fear modulation. These findings identify astrocytic Ca^{2+} signaling as a candidate mechanism for the astrocytic modulation of social-emotional behavior and point to a broader contribution of astrocytes to ASD-related behavioral dysfunctions, providing a basis for further mechanistic dissection of astrocyte-neuron interactions in ASD and related conditions.

Disclosures: N. Verda: None. **E. Van den Burg:** None. **S. Chattarji:** None. **R. Stoop:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.19/T2

Topic: B.09. Glial Mechanisms

Support: SUNDRY, Program for Neuropsychiatric Research

Title: Astrocyte-specific energetic dysfunction in iPSC derived models of schizophrenia

Authors: V. MCMAHON[1], E. KOH[1], V. SOOD[1], R. RAO[1], B. M. COHEN[2], *K. C. SONNTAG[1];
[1]Basic Neurosci. Dept., [2]Program for Neuropsychiatric Res., McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: There is growing evidence implicating dysregulations of cellular energetics in the pathology of schizophrenia (SZ). Astrocytes are one of the main regulators of brain metabolism, consuming most of the glucose used in the brain and shuttling lactate to neurons. Consequently, bioenergetic irregularities in astrocytes from SZ patients could be an underlying cause of altered metabolic brain functions and other downstream consequences, including abnormal synaptic activity. In this study, we investigated the metabolic profiles of astrocytes and neural precursor cells (NPCs) differentiated from SZ patients' and healthy control individuals' (HC) induced pluripotent stem cells (iPSC) to identify inherent bioenergetic dysfunctions. Through repeated Seahorse assays we found that under normoglycemic culture conditions, SZ-associated astrocytes demonstrated a reduced capacity to respond to metabolic stress compared to HC-associated astrocytes. Specifically, they exhibited lowered basal and maximum respiration, spare respiratory capacity, glycolysis, and respiratory and glycolytic stress responses, but an unchanged coupling effect, indicating a generalized respiratory and glycolytic energetic deficiency without compromised mitochondrial integrity. In contrast, SZ-associated NPCs presented similar metabolic profiles to HC-associated NPCs under resting and stress conditions, revealing that the bioenergetic deficits in SZ-associated cells are astrocyte-specific and emerge only after cell differentiation. HC- and SZ-associated astrocytes were then analyzed under hypoglycemic conditions with and without supplementation of the ketone body 3-hydroxybutyrate (3-OHB) to determine whether the cells could recover their lowered respiration by utilizing β-oxidation as an alternative energy source, as suggested by some clinical studies. We found no significant differences between HC- and SZ-associated astrocyte metabolism in hypoglycemia or with 3-OHB treatment. These data indicate that in normoglycemia, SZ-associated astrocytes are bioenergetically hypoactive, which could be due to lack of glucose uptake and/or processing limiting the availability of substrates to support mitochondrial respiration. In addition, astrocytes do not appear to benefit from supplementation with ketone bodies. Our findings are consistent with an increasing body of evidence showing that SZ is linked to impaired glucose uptake and metabolism and suggest that inherent bioenergetically dysfunctional astroglia may play a key role in SZ pathogenic processes.

Disclosures: V. McMahon: None. **E. Koh:** None. **V. Sood:** None. **R. Rao:** None. **B.M. Cohen:** None. **K.C. Sonntag:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.20/T3

Topic: B.09. Glial Mechanisms

Support: R01NS118066
Blazer Foundation

Title: ATL1 Mutation Drives NF-κB-Mediated Neuroinflammation and Synaptic Dysfunction in SPG3A Pathogenesis

Authors: *G. THAKUR[1], A. KHADILKAR[2], Z. CHEN[3], L. KONG[4], C. BLACKSTONE[5], S.-C. ZHANG[6], X.-J. LI[7];
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Abstract: Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurological disorders characterized by a length-dependent axonopathy of long corticospinal projection neurons. SPG3A, the most prevalent early-onset form of HSP, is caused by mutations in the *ATL1* gene, which encodes the atlastin-1 protein, leading to irregular cholesterol transfer from glial cells to cortical neurons. Despite established neuronal involvement, the role of astrocytes, critical regulators of brain homeostasis and inflammation, in SPG3A pathology remains largely unknown. This study investigates the role of ATL1 mutations in human astrocyte-driven neuroinflammation and neurodegeneration, links this to the co-activation of the NF-κB signaling pathway and evaluates the therapeutic potential of Liver X Receptor (LXR) agonists. Human pluripotent stem cells carrying *ATL1* mutations and their isogenic controls (H9) were differentiated into cortical astroglial cells via a multi-stage *in vitro* protocol involving embryoid bodies, neuroepithelial aggregates, and glial progenitors. Astroglial glutamate uptake functionality was quantified directly in isolated astrocytes. To assess the subsequent astroglial impact on neurodegeneration, mutated or control astrocytes were co-cultured with cortical neurons in different combinations. Neuronal synapsin protein expression and functional network activity were evaluated via immunostaining and calcium imaging, respectively. The anti-inflammatory effects of LXR agonists were evaluated by measuring pro-inflammatory IL-6 and TNF-α secretion via ELISA, while alterations in the NF-κB pathway were analyzed using ELISA and immunostaining. ATL1 mutations induce a reactive, pro-inflammatory phenotype in human astrocytes. Poly(I:C) (PIC) treatment significantly elevated IL-6 and TNF-α secretion in ATL1-mutated astrocytes compared to controls, a response that was successfully rescued by LXR agonist treatment. Furthermore, ELISA and immunostaining data confirmed prominent dysregulation of the NF-κB pathway in mutated cells. Importantly, *ATL1*-mutated astrocytes exhibited intrinsically impaired glutamate uptake. When placed in co-culture, these mutated astrocytes actively drove neurodegeneration, triggering a significant reduction in neuronal synapsin expression and disrupting functional calcium dynamics in the co-cultured neurons. Our findings demonstrate an astrocyte-mediated mechanism in SPG3A pathogenesis and highlight

LXR agonists as a promising therapeutic strategy to mitigate neuroinflammation and subsequent neurodegeneration.

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Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.21/T4

Topic: B.09. Glial Mechanisms

Title: Astrocytic calcium as an active controller of circuit excitability in a biophysically detailed primary motor cortex (M1) model: a framework for ALS-relevant maladaptive cortical networks.

Authors: *R. AZAB[1,3], E. URDAPILLETA[4,2,3], R. BARAVALLE[2,3], M. DE PITTÀ[5,6], A. DRANOVSKY[7,8], S. DURA-BERNAL[2,3,9];
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Abstract: Amyotrophic lateral sclerosis (ALS) is increasingly understood as a disorder of cortical circuit dysfunction, with altered excitability and calcium dysregulation in primary motor cortex (M1) emerging well before motor neuron loss. Astrocytes are vital modulators of intracellular signalling, affecting neural computation through two mechanistic routes. First, they exert fast synapse-proximal control, where astrocytic transporters and perisynaptic processes shape neurotransmitter clearance and diffusion, altering receptor activation, synaptic currents, and spike timing reliability. Second, astrocytes provide slower state-dependent control through intracellular signaling pathways that act as history-dependent regulators of synaptic efficacy and network activity. A hallmark of ALS pathology is loss of the astrocytic glutamate transporter EAAT2/GLT-1 (reduced 70-90% in ALS motor cortex and spinal cord), and mitochondrial dysregulation, elevating extracellular glutamate and driving cortical hyperexcitability and excitotoxicity. Existing computational models treat astrocytes as absent or passive, leaving no mechanistic account of how astrocytic calcium sets the rules for circuit stability or how disruption biases circuits toward instability. Moreover, integrating astrocytes into a biophysically detailed cortical circuit, i.e., spatial distribution, density, and connectivity between various cortical neurons remains unaddressed. We integrated a reaction-diffusion computational model of astrocytes using NEURON/RxD/NetPyNE to simulate intracellular calcium dynamics and extracellular glutamate signaling in a biophysically detailed mouse model of M1 circuits.

Astrocytes were embedded as an explicit spatial and signaling layer in the M1 model: number and placement are constrained by measured cortical densities and exclusive-domain tiling, and each domain is mapped onto the neurons and synapses it encloses to define cell-type-specific astrocyte-neuron coupling. We then close the tripartite loop with reaction-diffusion dynamics. Spike-timing and presynaptic firing-rate sweeps were characterized under graded astrocytic calcium states, demonstrating astrocytic coupling systematically shifts the calcium rate response curve relative to the uncoupled synapse. These results establish astrocytic calcium transients as active controllers of neural circuit stability regimes. The model provides a scalable, mechanistic substrate linking astrocytic dysfunction to maladaptive cortical networks in ALS and a foundation for integrating astrocyte-mediated coupling into large-scale circuit models of disease states.

Disclosures: R. Azab: None. **E. Urdapilleta:** None. **R. Baravalle:** None. **M. De Pittà:** None. **A. Dranovsky:** None. **S. Dura-Bernal:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.22/T5

Topic: B.09. Glial Mechanisms

Support: NIH Grant T32AG044402
NIH Grant 1R21NS125861-01
Packard Center for ALS Research at Johns Hopkins

Title: Contribution of astrocytic Sparcl1 to cortical synaptic dysfunction in C9orf72-FTD/ALS

Authors: *R. A. CULIBRK[1], L. M. GITTINGS[1], L. M. BUSTOS[1], B. ONDATJE[1], D. L. JULIAN[1], N. P. HANSEN[2], R. SHARMA[2], J. ANTONE[3], P. PIRROTTE[2], R. G. SATTLER[1]; [1]Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ; [2]Cancer and Cell Biol. Div., [3]Neurogenomics Div., The Translational Genomics Res. Inst., Phoenix, AZ

Abstract: Introduction. Recent studies suggest that altered astrocyte secretion of synaptogenic factors affects cortical neuronal viability and is a central driver of synaptic dysfunction in various neurodegenerative diseases. We previously demonstrated that one such factor, Sparcl1, is significantly reduced at the mRNA and protein levels in *C9orf72*-FTD/ALS (C9) postmortem frontal cortex tissues and patient iPSC-derived cortical astrocytes, respectively. Herein, we aim to assess (1) the impact of *SPARCL1* knockdown on human cortical astrocyte viability and function and (2) the electrophysiological consequences of modulating Sparcl1 levels within a human neuron-astrocyte coculture system.
Methods. Human primary cortical astrocytes (hCA) were stably transduced with doxycycline-inducible non-targeting or *SPARCL1* shRNA. Following, Day 3 i^{3}Neuron progenitor cells ($9x10^4$/well), with or without hCA ($4.5x10^4$/well), were spot-seeded into 48-well multielectrode

array plates (n = 8). Separately, Day 21 i^{3}Neuron monocultures received 10 or 100 nM recombinant human Sparcl1 (rhSparcl1) continuously during biweekly medium changes. Electrophysiological activity was recorded using the Axion Maestro system, and excitatory synaptic puncta colocalization (vGlut1/Homer1) was quantified using SynQuant.
Results. Continuous rhSparcl1 administration significantly increased the weighted mean firing rate (wMFR) and vGlut1/Homer1 colocalization of i^{3}Neuron monocultures in a dose-dependent manner ($p < 0.05$). Conversely, shRNA-mediated depletion of astrocytic *SPARCL1* significantly attenuated the ability of hCA to support long-term firing in i^{3}Neuron-hCA cocultures (~5-fold, $p < 0.05$). Finally, *SPARCL1* knockdown in hCA significantly altered cellular morphology, increased cytotoxicity measured via LDH, decreased glutamate uptake capacity, and altered the expression of multiple mRNAs associated with astrocyte reactivity and function.
Conclusion. Collectively, these findings suggest a crucial, cell autonomous requirement for astrocytic Sparcl1 in maintaining cytoskeletal integrity, metabolic viability, and glutamate homeostasis. They additionally support a critical role for Sparcl1 in excitatory synaptic development and maintenance and conversely suggest that its loss in C9 may contribute to astrocytic dysfunction, cortical synaptic degeneration, and neuron death.

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Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.23/T6

Topic: B.09. Glial Mechanisms

Support: NIEHS ES035043

Title: Genetic STING ablation attenuates astrocyte-mediated inflammation, neurotoxicity and motor dysfunction in the rotenone model of Parkinson's disease

Authors: *A. SCHULLER[1], O. YANOURI[2], A. BIBB[1], A. BRIGGS[3], M. HAGER[2], B. BAIRD[1], R. TJALKENS[1];
[1]Neurol., Barrow Neurolog. Inst., Phoenix, AZ; [2]ERHS, Colorado State Univ., Fort Collins, CO; [3]Neurosci., Arizona State Univ., Tempe, AZ

Abstract: Parkinson's disease (PD) is the fastest growing neurodegenerative disorder, linked with environmental risk factors including: air pollution, heavy metals, viral infections, industrial solvents, and pesticides. Our group has consistently shown the importance of inflammatory astro-glial activation in toxicant-induced pathogenesis of this condition. Most recently, the cGAS-STING pathway, which produces type-I-interferons in response to mislocalized dsDNA, has emerged as a potential disease-modifying therapeutic target. Efforts in this context have

largely focused on the role of microglial STING signaling; however, astrocytes are increasingly recognized as important contributors to parenchymal interferon levels. Here, we examined the effects of global STING knockout on motor function and astrocyte reactivity using the rotenone model of PD in wild-type (WT) and STING^{goldenticket} (GT) mice. Primary astrocyte-enriched mixed glial cultures were employed to establish the IC_{50}[Rotenone] = 78.90nM, which was blunted by pharmacologic STING inhibition and genetic ablation. Oxidative mtDNA damage was significantly increased following acute rotenone treatment via 8-OHdG quantification. High-content immunocytochemical fluorescence microscopy and deep learning-based image analysis revealed a subsequent increase in perinuclear p-STING^{+} puncta in GFAP^{hi}ALDH1L1^{hi} astrocytes, and STING-dependent nuclear p-IRF3^{+} translocation in the same dual-positive cell population downstream. Notably, co-treatment with the VDAC inhibitor DIDS blunted rotenone-induced NF-kB activation and IFN-β production. Further mechanistic interrogation revealed a STING-dependent enrichment of MAPK signaling and ECM remodeling via transcriptomics, as well as astrocytic secretion of TNF-α, VEGF, and IL-6, which were all blunted in GT cells. Collectively, this resulted in a STING-dependent astrocyte-mediated neurotoxic effect on dopaminergic neuron-like cells treated with glial conditioned media. *In vivo*, automated gait assessment demonstrated time-, treatment-, and genotype-dependent hypokinesia in WT mice that was attenuated in GT mice. Concordantly, HPLC-ECD neurochemical profiling revealed male-specific depletion of striatal dopamine and increased turnover of this metabolite, which was attenuated by genetic STING ablation. Together, these data demonstrate the importance of cGAS-STING signaling in inflammatory astrocyte reactivity, dopaminergic neurotoxicity, and PD-like motor dysfunction. Future work will interrogate the effects of astrocyte-specific STING ablation on PD-relevant neuropathologic outcomes.

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Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR301.24/T7

Topic: B.09. Glial Mechanisms

Title: Examining the role of Astrocyte-Derived YKL-40 During Cuprizone-Induced De/Remyelination

Authors: *S. MUNIR, J. GONZALES, S. SINGH;
Virginia Commonwealth Univ., Richmond, VA

Abstract: Multiple sclerosis (MS) is a neurodegenerative disease affecting approximately 2.9 million people worldwide, characterized by myelin loss and cognitive decline. Among others, neuroinflammation, reactive astrocytes, and microglia are hallmarks of MS and may contribute to the de/remyelination. Interestingly, cerebrospinal fluid levels of YKL40, also known as

CHI3L1, are elevated in individuals with multiple sclerosis, yet its role during de/remyelination is not clear. Previously, our lab identified YKL40 as an astrocyte-secreted factor whose expression is increased during developing brain and in neuroinflammation. However, its role in de/myelination remains unclear. To investigate this, we generated a tamoxifen-inducible astrocyte specific YKL-40 knockout mouse model and subjected it to a well-established cuprizone-induced de/remyelination model. Brain tissue from mice was analyzed using qPCR, RNA sequencing, and immunofluorescence to assess neuroinflammatory and de/remyelination-associated markers. Our data indicate that loss of astrocytic YKL-40 exacerbates neuroinflammation and may worsen demyelination. Our ongoing efforts will further identify important roles of astrocytic YKL-40 during de/remyelination, potentially offering therapeutics for MS and other demyelinating disorders.

Disclosures: S. Munir: None. **J. Gonzales:** None. **S. Singh:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

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Program #/Poster #: PSTR301.25/T8

Topic: B.09. Glial Mechanisms

Support: NIH intramural research program 1ZIANS003137

Title: Glial fatty acid binding protein is a novel injury-response factor involved in axonal debris clearance

Authors: *J. TABET[1], J. YIN[2], Q. YUAN[3];
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Abstract: After central nervous system (CNS) injury, restoration of the lipid microenvironment is crucial for repair. Fatty acids (FAs) play an essential role in cell and tissue functioning, yet they can also contribute to lipid toxicity and neuroinflammation after neural injury, ultimately impeding recovery. In physiological and pathological states, fatty acid binding proteins (FABPs) transport FAs for clearance, storage, and metabolic homeostasis. We previously identified Obp44a as a glia-secreted FABP highly expressed in the *Drosophila* CNS that traffics long-chain FAs between neurons and glia. Through genetic manipulation and *in vivo* imaging, we demonstrated that Obp44a facilitates lipid debris clearance during development and is recruited after axonal injury. In the current study, we seek to understand how FABPs contribute to axonal degeneration and clearance and the downstream lipid waste management mechanisms. Using established markers of Wallerian degeneration and glial activation, we characterized the spatiotemporal dynamics of Obp44a following axonal injury using an Obp44a-GFP knock-in allele. We found that Obp44a localizes to injured axon terminals and its accumulation closely parallels the time course of axonal degeneration and glial engulfment, peaking 24 hours after

injury. Additionally, by analyzing the *highwire* null mutant, we demonstrate that the Obp44a injury response is markedly reduced in the absence of axonal degeneration, suggesting that Obp44a, potentially through its fatty acid-binding properties, contributes to degeneration-associated neuron-glia interactions elicited by the injury. Together, these results establish Obp44a as a novel injury-responsive factor and provide a foundation for investigating how FABPs regulate glial responses to axonal degeneration. Ongoing studies will further probe Obp44a and other FABPs' functions in CNS injury and recovery by monitoring debris clearance and stress response, as well as downstream FA engulfment and processing within glia.

Disclosures: J. Tabet: None. **J. Yin:** None. **Q. Yuan:** None.

Poster

PSTR301: Astrocytes: Reactivity and Mechanisms of Neurological Disease

Location: WCC Halls A-C

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Program #/Poster #: PSTR301.26/T9

Topic: B.09. Glial Mechanisms

Support: NIH Grant 1R21NS131634 (NINDS)

Title: Astrocytic HIF-1α suppresses frataxin to drive white matter injury and cognitive dysfunction in sickle cell disease

Authors: *R. HAZRA[1], S. LENHART[4], P. MONDAL[5], E. MICHAUD[2], L. M. FOLEY[1], T. K. HITCHENS[6], S. GHOSH[2], X. HU[3];
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Abstract: Cerebrovascular injury in sickle cell disease (SCD) drives a high burden of white matter abnormalities, silent cerebral infarction, and neurocognitive impairment. A central but incompletely understood driver of these complications is recurrent hypoxia/reoxygenation (H/R), which reflects the bidirectional pathobiology of SCD. While hypoxia promotes cerebral oxygen deprivation, reoxygenation amplifies oxidative stress, endothelial inflammation, and neurovascular instability. Since SCD brain operates near cerebral oxygen reserve limits, repeated H/R episodes may damage white matter regions vulnerable to hypoperfusion. Astrocytes, located at the neurovascular interface, regulate cerebral blood flow and synaptic plasticity. We identified astrocytic frataxin (FXN) as a key regulator of diffusion tensor imaging (DTI) detectable white matter injury (WMI), neuroaxonal damage, astrocyte activation, and cognitive impairment in sickle mice (PMID: 42037666). These findings led us to hypothesize that H/R-induced stabilization of hypoxia-inducible factor-1α (HIF-1α) represses astrocytic FXN, thereby disrupting astrocyte-neuron homeostasis and promoting WMI.To test this mechanism, we crossed Hif1α-floxed mice with Aldh1l1-Cre/ERT2 mice to generate tamoxifen-inducible astrocyte-specific HIF-1α knockout mice. We transplanted wild-type and astrocytic HIF-1α -deficient recipients with sickle bone marrow to generate SCD chimeras with intact ($SS^{Hif1\alpha}$) or

deleted astrocytic HIF-1α (SS $^{ASHif1\alpha KO}$). We evaluated white matter integrity by DTI and studied mice under normoxic and H/R conditions using novel object recognition and Y-maze testing to assess learning and spatial working memory. We also tested whether pharmacologic or siRNA-mediated HIF-1α inhibition restores FXN during hypoxic stress in human primary astrocytes.SCD chimeras with intact astrocytic HIF-1α displayed reduced FXN expression ($n=5$, $p<0.05$), increased astrocyte activation ($n=6$, $p<0.05$), impaired novel object recognition and Y-maze performance ($n=15$, $p<0.001$), and evidence of WMI following H/R. In contrast, astrocyte-specific HIF-1α deletion preserved astrocytic FXN ($n=5$, $p<0.01$), improved cognitive responses ($n=15$, $p<0.05$), and attenuated H/R-associated neuroaxonal injury. In human primary astrocytes, HIF-1α inhibition mitigated FXN suppression and altered downstream calcium-associated mGluR5, GLAST, and NMDA signaling implicated in astrocyte activation and synaptic dysfunction.Together, these findings identify astrocytic HIF-1α as an upstream target that may offer a disease modifying strategy to preserve neurocognitive function in SCD.

Disclosures: R. Hazra: None. **S. Lenhart:** None. **P. Mondal:** None. **L.M. Foley:** None. **T.K. Hitchens:** None. **S. Ghosh:** None. **X. Hu:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.01/T10

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

Support: NIH P01AG014449
NIH R01AG081286
BrightFocus Foundation CA2018010
Barrow Neurological Foundation
Arizona Alzheimer's Consortium

Title: Cytochrome c and tau pathology in the frontal cortex of Individuals with Down syndrome with and without dementia

Authors: *S. E. PEREZ, J. MIGUEL, E. J. MUFSON;
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Abstract: Down syndrome (DS) is characterized by developmental delays and intellectual disability caused by triplication of chromosome 21 (Chr21). By their forties, virtually all individuals with DS exhibit amyloid-β (Aβ) plaques and phosphorylated tau (p-tau)-bearing neurofibrillary tangles (NFTs); however, only approximately two-thirds develop Alzheimer's disease-type dementia (DSD+). Previously, we demonstrated that the frontal cortex (FC) of demented DS individuals exhibits greater NFT burden and more advanced tau pathology compared with non-demented DS cases (DSD-), suggesting a critical role for tau pathology in dementia development in DS. Individuals with DS also display mitochondrial dysfunction due to

overexpression of Chr21 genes (e.g., *SOD1, APP, RCAN1, DYRK1A, NRIP1, SUMO3, CBS, ETS2, ITSN1,* and *PKNOX1*), which disrupt oxidative phosphorylation through alterations in electron transport chain (ETC) proteins and ATP production. Whether ETC dysfunction differs during NFT evolution between DSD+ and DSD- individuals remains unknown. Here, we used quantitative densitometric immunofluorescence to characterize ETC protein alterations and tau pathology in FC tissue from DSD+ and DSD- cases. We assessed the ETC electron carrier cytochrome c (Cyt c), ATP synthase subunit alpha (ATP5A1), early tau phosphorylation (AT8), tau truncation (TauC3), and the neuronal marker microtubule-associated protein 2 (Map2). Optical density (OD) and cellular area were measured in FC layer V-VI projection neurons immunostained for Cyt c, ATP5A1, and Map2, in the presence or absence of AT8 and TauC3 pathology. We found significantly higher Cyt c OD in neurons lacking tau pathology as well as in AT8- or TauC3-positive neurons in DSD- compared with DSD+ cases, whereas ATP5A1 levels did not differ between groups. In DSD+ cases, Cyt c, ATP5A1, and Map2 OD were significantly reduced in AT8- and TauC3-positive neurons compared with neurons lacking tau pathology. Additionally, Cyt c, but not Map2, immunoreactive area was significantly greater in neurons lacking AT8 pathology in DSD- compared with DSD+ cases; no such difference was observed for ATP5A1. These findings suggest that preserved Cyt c expression, but not ATP5A1, in FC projection neurons of non-demented individuals with DS supports greater mitochondrial function and energy production. This mitochondrial resilience may contribute to resistance against tau-associated neurodegeneration, cognitive decline, and dementia in DS.

Disclosures: S.E. Perez: None. **J. Miguel:** None. **E.J. Mufson:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.02/T11

Topic:

Support: NIH P01AG014449
NIH RF01G081286
NIH P30AG010161
Arizona Alzheimer's Consortium
Barrow Neurological Foundation

Title: Mitochondrial metabolic upregulation in the frontal cortex in very old individuals with superior cognitive abilities

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Abstract: Adults aged 80 years and older whose episodic memory performance surpasses that of age-matched peers and remain comparable to individuals 20-30 years younger represent a

growing segment of the aging population, yet the factors that support their superior cognitive function remain an under investigated area. Although studies highlighted a key role for mitochondria, the powerhouse of cellular function, in longevity and healthy aging, its role in the preservation of superior memory in very old individuals remains largely unexplored. Here, we investigated mitochondrial metabolism in the frontal cortex (FC) of non-demented individuals aged 80 years and older whose episodic memory performance was superior to that of normal cognitive performers. Participants were identified based upon the last available Wechsler Memory Scale-Revised Logical Memory Delayed Recall (LM-DR) score obtained prior to death from non-cognitively impaired participants of the Rush Religious Orders study (Malek-Ahmadi et al., 2026). Here, FC protein levels were measured by western blot in 22 individuals classified as superior cognitive performers (SCP; LM-DR ≥14) and 17 normal cognitive performers (NCP; LM-DR 13-7) for markers associated with mitochondrial biogenesis (PGC-1α, NRF1, NRF2, TFAM, Sirtuin 1), mitophagy (FUNDC1, BNIP3L/NIX, DRP1), energy production (lactate dehydrogenase A [LDHA], lactate dehydrogenase B [LDHB]), and calcium signaling (BAP31, VDAC1, MFN2, GRP75, PTPIP51), all critical regulators of mitochondrial homeostasis known to be impaired during aging. SCP cases compared to NCP exhibited significantly higher levels of the mitochondrial biogenetic proteins NRF1, NRF2, and Sirtuin 1, whereas PGC-1α and TFAM levels were unchanged. The mitophagy receptor BNIP3L/NIX was significantly elevated in SCP, while FUNDC1 and the mitochondrial fission protein DRP1 were preserved across groups. Levels of LDHA and LDHB were significantly increased in SCP. Among the mitochondria-associated membrane proteins involved in calcium transport, MFN2 and GRP75 were significantly upregulated in SCP, whereas BAP31, VDAC1, and PTPIP51 levels did not differ between groups. Correlation analyses revealed significant positive associations between LM-DR scores and NRF1 and NRF2 across cognitive groups. Episodic memory performance was also positively correlated with NRF1 and MFN2. In contrast, BNIP3L/NIX levels negatively correlated with Braak stage and total neurofibrillary tangle burden. These findings suggest that enhanced mitochondrial function plays a key role in the maintenance of superior cognition in very old individuals.

Disclosures: E.J. Mufson: None. **B. He:** None. **M. Malek-Ahmadi:** None. **S.E. Perez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.03/T12

Topic:

Support: NIH P01AG014449
NIH R01G081286
NIH P30AG010161
Arizona Alzheimer’s Consortium
Barrow Neurological Foundation

Title: U1-70K splicing protein reduction occurs early within cholinergic neurons in the nucleus basalis in Alzheimer's disease

Authors: *M. MORENO-RODRIGUEZ[1], M. NADEEM[1], M. MALEK-AHMADI[2], E. J. MUFSON[1], S. E. PEREZ[1];
[1]Barrow Neurolog. Inst., Phoenix, AZ; [2]Banner Alzheimer's Inst., Glendale, AZ

Abstract: Given the limited efficacy of current therapeutic approaches for Alzheimer's disease (AD), there is a critical need to identify novel molecular targets involved in disease onset and progression. The spliceosome, a dynamic macromolecular complex responsible for pre-mRNA processing, has been increasingly associated with AD pathophysiology. Previous studies from our laboratory have identified splicing alterations in cortical cholinergic projection areas in the early AD; however, the contribution of spliceosome dysfunction to cholinergic basal forebrain (CBF) degeneration remains poorly understood. Here, we investigated alterations in the splicing proteins U1-70K and U1A, two core components of the U1 snRNP complex, as well as SRSF2, an alternative splicing factor, and hnRNPA2B1, a regulator of pre-mRNA splicing in postmortem tissue containing CBF neurons located with the anterior and lateral subfields of the nucleus basalis of Meynert from participants of the Rush Religious Orders Studies cohort with a premortem clinical diagnosis of no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD using immunohistochemistry, immunofluorescence, and western blotting. We found a significant reduction in U1-70K nuclear intensity and area in CBF neurons in MCI and AD compared to NCI, which positively correlated with multiple cognitive domains. Although U1A, SRSF2, and hnRNPA2B1 nuclear area significantly decreased in MCI and AD compared to NCI, nuclear intensity was unchanged, whereas nuclear area correlated with cognitive parameters. Despite changes in nuclear area with disease progression, the soma area of $p75^{NTR}$-positive neurons remained stable across disease stages. Immunoblot analysis revealed no group changes for any of the splicing proteins analyzed. By contrast, $A\beta_{1-42}$ plaque burden in the basal forebrain was significantly higher in AD than in MCI, whereas neither AT8-positive neurons nor neuropil threads differed between groups. Neither amyloid nor tau pathologies were associated with alterations in splicing proteins. Overall, our findings suggest that selective loss of U1-70K in CBF neurons and nuclear area reductions are early events during AD that occurred independently of classical AD pathology and may contribute to CBF pathophysiology in AD.

Disclosures: M. Moreno-Rodriguez: None. **M. Nadeem:** None. **M. Malek-Ahmadi:** None. **E.J. Mufson:** None. **S.E. Perez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.04/T13

Topic:

Support: NIA AG014449
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NIA AG077103
NIA AG085572

Title: Hippocampal neuron populations exhibit unique RNA-sequencing profiles in human Down syndrome with Alzheimer's disease pathology

Authors: *S. D. GINSBERG[1,2,3,4], H. PIDIKITI[1], K. W. IBRAHIM[5], S. LEE[1,2], G. CHIOSIS[6,7], E. J. MUFSON[8], G. E. STUTZMANN[9], M. J. ALLDRED[1,2];
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Abstract: Individuals with Down syndrome (DS) present with phenotypic alterations including behavioral and cognitive impairments along with lifelong intellectual disability. During mid-life individuals with DS display extensive amyloid plaques, neurofibrillary tangle formation, synaptic loss, inflammation, and neocortical and hippocampal atrophy similar to Alzheimer's disease (AD). Since the lifespan of individuals with DS extends into the 5^{th}-6^{th} decades of life, an increase in dementia associated with AD (DS+AD) is prevalent. However, cellular mechanism(s) driving neuronal dysfunction in the DS and DS+AD brain are poorly understood. We examined single populations of selectively vulnerable hippocampal neurons to elucidate alterations that may advance development of therapeutic targets for early intervention. Postmortem human hippocampal CA1 pyramidal neurons and dentate gyrus granule cells (DGCs) were interrogated via laser capture microdissection combined with single population RNA-sequencing from aged individuals with DS having confirmed AD pathology (DS+AD) compared to age-matched and sex-matched controls (CTRs). Bioinformatic inquiry identified differentially expressed genes (DEGs) and relevant biological pathways for each hippocampal neuron population in the DS+AD cohort compared to CTRs. Interrogating DEGs and downstream pathways in both CA1 pyramidal neurons and DGCs in postmortem DS brain revealed an overall dysregulation mosaic that is neurodegenerative in nature, with both overlapping and unique patterns of dysregulation, reflecting intrinsic similarities, as well as differences, in these excitatory hippocampal neurons. DEG to pathway correlations were used to identify novel targets of dysregulation in this DS+AD disease phenotype that are candidates for therapeutic intervention in the context of DS which also informs AD.

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Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.05/T14

Topic:

Support: AG014449
AG072599
AG074004
AG077103
AG085572

Title: Comparison analysis of single population RNA-sequencing profiles in excitatory cortical and hippocampal neuron populations from Down syndrome with Alzheimer's disease (DS+AD)

Authors: *M. J. ALLDRED[1,3], H. PIDIKITI[1], S. D. GINSBERG[2,3];
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Abstract: Down syndrome (DS), caused by triplication of human chromosome 21 (HSA21), represents the primary genetic cause of intellectual disability. Individuals with DS have developmental delays and neurological deficits which increase during mid-life with the development of Alzheimer's disease (AD) pathology. Individuals with DS develop profuse amyloid plaques, neurofibrillary tangle formation, basal forebrain cholinergic degeneration, synaptic loss, inflammatory changes as well as neocortical and hippocampal thinning and atrophy, with AD dementia the leading cause of death in adults. We posit gene expression signatures extending beyond HSA21 triplication that causes DS drive dysregulation in neuron populations vulnerable to AD degeneration. We microisolated excitatory neuron populations from frontal cortex Brodmann area 9 (BA9, layer III and layer V pyramidal neurons; PNs) and hippocampus {e.g., CA1 PNs and dentate gyrus granule cells (DGCs)} via laser capture microdissection and performed single population RNA-sequencing (RNA-seq) with downstream bioinformatic inquiry. These spatially characterized neuron populations generated unique expression profiles in human postmortem tissue from DS+AD cases compared to age-matched and sex-matched controls (CTR). We observed both convergent and divergent expression profiles in each individual neuron population. To determine if diverse spatially localized neurons share genes and/or biological pathways that may drive overall pathology, correlation analysis was performed on the resulting gene expression profiles. Results indicated varying correlation between neuron populations, suggesting circuitry inputs as well as individual neuronal vulnerability impacts cellular mechanisms of degeneration. Triplicated HSA21 genes were significantly upregulated in a circuitry dependent manner, with each excitatory neuron population having a unique HSA21 mosaic, validating our hypothesis of intrinsic neuronal vulnerability. Pathway analyses implicate bioenergetic fitness, synaptic transmission, and RNA metabolism, among others in excitatory neuron degeneration. Further bioinformatic and pathway analyses will pinpoint targets of interest across and within these neuronal populations to identify viable targets for therapeutic intervention.

Disclosures: M.J. Alldred: None. **H. Pidikiti:** None. **S.D. Ginsberg:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.06/T15

Topic:

Support: Institute for Social Science Research
Arizona Department of Health Sciences (ADHS14-052688)
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Arizona Alzheimer's Disease Research Center REC Fellows Program and Arizona Alzheimer's Consortium
PPG: NIA P01AG14449

Title: Cerebellar synaptic dysfunction and structural plasticity in Alzheimer's Disease

Authors: *A. YERRAMILLI[1], A. HASHIM[1], E. J. MUFSON[2], S. E. PEREZ[2], J. L. VERPEUT[1];
[1]Arizona State Univ., Tempe, AZ; [2]Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with synaptic dysfunction and neurodegeneration. Although AD pathology has been extensively studied in cortical and hippocampal regions, the cerebellum remains relatively understudied despite growing evidence supporting its role in cognitive function. Previous work from our laboratory using postmortem cerebellar tissue from participants in the Rush Religious Orders Study (RROS) with premortem clinical diagnoses of no cognitive impairment (NCI), mild cognitive impairment (MCI), and Alzheimer's disease (AD) revealed compromised myelin integrity in the cerebellum of AD patients. Specifically, we found that the optical intensity of myelin basic protein (MBP), a key component involved in maintaining the multilayered axonal myelin sheath, was significantly reduced in both the cerebellar white matter (Mann-Whitney test, AD vs NCI: $p = 0.0232$) and the cerebellar granule cell layer (AD vs NCI: $p = 0.0015$; AD vs MCI: $p=0.0028$) of AD cases. Furthermore, MBP intensity in the granule cell layer was positively associated with global cognitive scores, episodic memory, visuospatial performance, and Mini-Mental State Examination (MMSE) scores, and negatively associated with Braak stage and amyloid plaque burden. These findings indicate a selective vulnerability of the cerebellum in AD and provide the rationale for the current investigation examining synaptic integrity and neuronal structural plasticity during AD progression. To achieve this, formalin-fixed, paraffin-embedded cerebellar sections from NCI, MCI, and AD cases were immunostained for the presynaptic markers synaptophysin and α-synuclein, the dendritic spine-associated protein drebrin, and the structural neuronal marker microtubule-associated protein 2 (MAP2). To quantitatively and qualitatively assess changes in the expression of these proteins across the different cerebellar layers during AD progression, whole-slide images were acquired using a

brightfield scanner and analyzed with QuPath software. These ongoing analyses are designed to determine whether markers of dendritic spine plasticity and neuronal structure precede changes in presynaptic markers during the transition from normal cognition to MCI and AD. Together, these studies extend our previous findings and will provide new insights into the relationship between synaptic integrity, structural plasticity, and disease progression in AD.

Disclosures: A. Yerramilli: None. **A. Hashim:** None. **E.J. Mufson:** None. **S.E. Perez:** None. **J.L. Verpeut:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

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Program #/Poster #: PSTR302.07/T16

Topic:

Support: NIH/NIA R01 AG059627
NIH T32 AG082658

Title: Elevated ITSN1 as a link between endosomal disruption and neurodegeneration in Down syndrome and Alzheimer's Disease

Authors: *S. TALLINO[1,2], J. NEWBERN[1,2,3], R. VELAZQUEZ, Jr.[1,2,3];
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Abstract: Early endosomal dysfunction is increasingly implicated in neurodegeneration, but mechanisms linking altered endocytic regulation to cellular vulnerability remain unresolved. In Down syndrome (DS), individuals exhibit hallmark Alzheimer’s Disease (AD) pathology by age 40, preceded by early cellular abnormalities including endosomal enlargement and intracellular amyloid accumulation. In both DS and AD, the basal forebrain (BF) shows volume loss via imaging and cholinergic neuron loss in post-mortem tissue that correlates with cognitive decline. The Ts65Dn mouse model of DS also exhibits loss of BF cholinergic neurons (BFCNs), which demonstrate enlarged early endosomes with age as Aβ accumulates. The goal of this project is to determine the role of Intersectin 1 (ITSN1) in endosomal enlargement and cell loss in Ts65Dn mice. ITSN1 is a scaffolding-associated protein integral to endosomal trafficking which is triplicated in DS and elevated in AD. Further, perinatal dietary interventions that prevent BFCN decline in Ts65Dn mice lower ITSN1 levels and restore early endosome size in BFCNs. We now show that ITSN1 expression is increased in human AD (n = 97) versus age-matched controls (n = 98), balanced for sex, and that ITSN1 levels are elevated in BF homogenates from 8mo old Ts65Dn (n = 12 animals/genotype, sex balanced). We then investigated whether adeno-associated virus (AAV)-mediated delivery of an ITSN1-targeting short hairpin RNA (shRNA) in the adult BF prior to the onset of BFCN loss, would be sufficient to prevent endosome enlargement, BFCN loss, and BFCN-dependent behaviors. We stereotactically injected the

AAV.PHP.eB serotype carrying GFP and either a scrambled sequence (AAV-scrmbl) or the ITSN1 shRNA (AAV-ITSN1) into the medial septum of the BF at 3.5mo old (n = 8-14 per sex, genotype, and virus). BF-modulated behaviors were tested at 11mo old, and tissues were subsequently collected for immunohistochemical and other analyses at 11.5mo. Preliminary results suggest reductions in ITSN1 in the BF of AAV-ITSN1 mice relative to controls. Further, AAV-ITSN1 mice showed slight but significant improvements in rotarod performance and completed more correct trials in the radial arm water maze, with additional analyses ongoing to determine if ITSN1-mediated endosomal alterations coincide with these behavioral improvements. Understanding the early pathological events that are common to both AD and DS may provide future cognition-relevant therapeutic targets.

Disclosures: S. Tallino: None. **J. Newbern:** None. **R. Velazquez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

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Arizona Biomedical Research Commission (contracts 4001, 0011, 05-901 and 1001 to the Arizona Parkinson's Disease Consortium)
Michael J. Fox Foundation for Parkinson's Research

Title: Targeting Dyrk1a in Alzheimer's Disease: single-nucleus RNA sequencing data reveals broad effects across CNS cell populations

Authors: *S. K. BARTHOLOMEW[1,2], W. WINSLOW[1], Q. WANG[1], C. HULME[3,4], T. DUNCKLEY[1], R. VELAZQUEZ, Jr.[1,2];
[1]Neurodegenerative Dis. Res. Ctr., [2]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [3]Div. of Drug Discovery and Development, Dept. of Pharmacol. and Toxicology, [4]Dept. of Chem. and Biochemistry, Col. of Sci., Univ. of Arizona, Tucson, AZ

Abstract: The prevalence of Alzheimer's Disease (AD) and Related Dementias (ADRD) increase annually, emphasizing a need for effective therapeutic interventions. Developing therapeutics that target proteins contributing to multiple aspects of pathogenesis would be most efficacious. One targetable protein is Dual-specificity tyrosine-phosphorylation related kinase 1a (Dyrk1a) which contributes to both amyloid (Aβ) and tau pathogenesis and is involved in RNA splicing and synaptic function. We found higher Dyrk1a protein levels in primary tauopathies, and AD postmortem brains compared to healthy controls, supporting Dyrk1a as a therapeutic target. Our group developed a novel inhibitor named DYR533, which reduced neuropathology in three mouse models of ADRD (3xTg-AD, PS19, and Ts65Dn). Under basal conditions, Dyrk1a is highly expressed in microglia and neurons, but little is known about its cells-specific functions nor how they change across disease. Here, we took an in depth look at *DYRK1A* expression in single-nuclear resolution across AD progression by querying single-nucleus RNA sequencing (snRNAseq) data from human postmortem brain tissues. SnRNAseq data from the prefrontal cortex region of 427 individuals in the ROSMAP cohort with a full spectrum of neuropathologies and clinical manifestations were downloaded from the AD-knowledge portal (syn52293417). We adopted a pseudobulk approach to generate a count matrix for each cell type by extracting counts of the cell type and aggregating them per gene per individual. Low-expression genes were filtered out using edgeR. Pseudobulk counts were normalized via the trimmed mean of M-values method; the log2 of counts per million mapped reads was computed using limma. Expression levels were then quantile-normalized. Levels within each cell type were linearly regressed with neuropathological and clinical data. *DYRK1A* was found to be highly expressed across all cell types with a trend of increased expression in the neuropathologically confirmed AD subjects in almost all cell types. At the pseudobulk level, its expression was significantly associated with both Aβ and tangles in excitatory neurons, as well as in the domain of episodic memory and, suggestively, semantic memory. These data implicate *DYRK1A* in AD progression, providing complementary evidence to our findings at the protein level. Cell-specific expression of *DYRK1A* across disease may provide insight into vulnerable cell classes and how changes impact specific mechanisms driving disease.

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Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.09/T18

Topic:

Title: Brain Choline Deficiency in Primary Tauopathies and Therapeutic Benefits of Choline Supplementation in PS19 Mouse Model of Tauopathy

Authors: *W. WINSLOW[1], A. MARTIN[1], J. M. JUDD[1], S. K. BARTHOLOMEW[1], G. E. SERRANO[2], T. G. BEACH[2], R. VELAZQUEZ, Jr.[1];
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Abstract: The role of environmental factors in tauopathies remains poorly understood. Primary tauopathies are neurodegenerative disorders driven by tau pathology, including Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Pick's disease, and Frontotemporal Dementia (FTD). In contrast, secondary tauopathies, such as Alzheimer's disease (AD), develop when tau abnormalities arise secondary to another disease process. Although some cases are genetic, most are sporadic, suggesting environmental contributions to risk. Homocysteine (Hcy), a diet-modifiable amino acid elevated in tauopathies, promotes tau pathology by increasing activity of the tau kinases glycogen synthase kinase 3β and cyclin-dependent kinase 5. Choline intake lowers Hcy, yet most adults do not meet recommended levels. Choline is converted to betaine, a methyl donor for Hcy remethylation to methionine, and supports membrane phospholipid synthesis, epigenetic regulation, and acetylcholine production for memory and cognition. Choline deficiency exacerbates inflammation, amyloid-β accumulation, and tau pathology, whereas supplementation reduces inflammation and amyloidosis. However, brain choline status in primary tauopathies, and the impact of deficiency or supplementation on disease progression, remain unclear. We quantified choline levels in postmortem superior frontal gyrus tissue, a region vulnerable to primary tauopathies, from individuals with PSP, CBD, and Pick's disease, and age-matched controls (n = 4-8/group). To test dietary effects, PS19 (P301S tau) and wild-type mice were fed choline-deficient (0.5 g/kg), adequate (1.1 g/kg), or supplemented (5.0 g/kg) diets from 3-9 months. We assessed spatial cognition (Barnes maze), circulating choline, hippocampal tau phosphorylation at threonine 181 (T181) and serine 396 (S396), and plasma biomarkers GFAP (astroglial activation) and neurofilament light chain (NfL; axonal injury). Primary tauopathy cases had significantly lower brain choline than controls. In mice, circulating choline reflected dietary intake. In PS19 mice, choline deficiency elevated hippocampal tau hyperphosphorylation at T181 and S396 and increased plasma GFAP and NfL. In contrast, supplementation partially rescued spatial cognition, reduced tau hyperphosphorylation, and lowered GFAP and NfL. These bidirectional effects were more pronounced in females. Collectively, these findings identify choline deficiency as a feature of primary tauopathies and support choline supplementation as a potential therapeutic strategy, warranting future investigation in humans.

Disclosures: W. Winslow: None. **A. Martin:** None. **J.M. Judd:** None. **S.K. Bartholomew:** None. **G.E. Serrano:** None. **T.G. Beach:** None. **R. Velazquez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.10/T19

Topic:

Support: ASU Startup
ASU Edson seed

Title: Repurposing the FDA-approved alpha-glucosidase inhibitor miglitol for Alzheimer's disease: Effects in APOE3/E4 brain organoids and 3xTg-AD mice

Authors: *W. H. GENDRON[1], L. T. FENG[2,3,4,5], W. WINSLOW[1], V. UMAIYALAN[2,3,4,5], R. T. GAIKWAD[2,3,4,5], R. CHAN[4,5], Q. WANG[1], E. T. LIM[2,3,4,5], R. VELAZQUEZ, Jr.[1,6]; [1]ASU-Banner Neurodegenerative Dis. Res. Ctr., Tempe, AZ; [2]Med., [3]Molecular, Cell and Cancer Biol., [4]Neurol., [5]NeuroNexus, Univ. of Massachusetts Chan Med. Sch., Worcester, MA; [6]Sch. of Life Sci., Arizona State Univ., Tempe, AZ

Abstract: Introduction: Efforts to repurpose FDA-approved therapies have emerged as a strategy to find alternative disease-modifying treatments for AD. We recently identified the diabetics drug target α-glucosidase MGAM as a novel drug repurposing target for AD. Miglitol (MIG), an MGAM inhibitor, may provide neuroprotective benefits by restoring systemic metabolic balance. Individuals carrying the APOE4 allele are at a higher risk for developing AD and are vulnerable to metabolic and inflammatory stressors. Targeting peripheral physiology is a promising therapeutic strategy because systemic metabolic dysfunction often precedes and accelerates AD pathology. We therefore investigated whether MIG reduces AD-related neuropathological and inflammatory markers in APOE33 (E33) vs E44 (E44) human AD brain organoids and in 3xTg-AD mice. **Methods:** We differentiated 7-month-old 2D dissociated cells from cerebral organoids (dcOrgs) using induced pluripotent stem cells from E33 or E44 donors. 200uM of MIG treatment was introduced to mock dcOrgs or herpes simplex virus 1 (HSV-1) infected dcOrgs that model neuroinflammation associated with AD *in-vitro*. These samples were RNA sequenced. In parallel, at 7.5 months of age, 3xTg-AD mice received oral administration of vehicle, 10 or 30 mg/kg of MIG for 30 consecutive days (n = 3–4 per group; sex-balanced cohorts). We used Enzyme-linked immunosorbent assays to quantify plasma glial fibrillary acidic protein (GFAP), a marker of neuroinflammation, neurofilament light chain (NfL), a marker of neuroaxonal injury, and AD–related pathological markers, including soluble (sol) and insoluble (insol) Aβ40 and Aβ42 and phosphorylated tau (pTau Serine (S) 396, Threonine (T)231, and T217). **Results:** MIG treatment on HSV-1-infected dcOrgs had significantly more differentially expressed genes (DEGs) in E33 compared to E44. Several MGAM downstream target genes were solely rescued in MIG-treated and infected E33 dcOrgs. No differences in DEGs were seen between MIG treated mock E44 and E33 dcOrgs, indicating that the effects of MIG occur only in HSV-1-infected dcOrgs. MIG treatment at 30 mg/kg was the most effective at decreasing sol and insol Aβ40 and Aβ42 in 3xTg-AD mice. In females, 30 mg/kg MIG reduced sol and insol pTau T217, as well as insol T231 and S396. At 30 mg/kg, males showed a reduction in insol S396. GFAP and NfL were significantly reduced with treatment, highlighting blood-based biomarker tracking to monitor treatment-associated changes. **Conclusion:** These findings support the repurposing of MIG as a strategy for AD that may confer meaningful neuroprotective effects in the degenerating brain.

Disclosures: W.H. Gendron: None. **L.T. feng:** None. **W. Winslow:** None. **V. Umaiyalan:** None. **R.T. Gaikwad:** None. **R. Chan:** None. **Q. Wang:** None. **E.T. Lim:** None. **R. Velazquez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.11/T20

Topic:

Support: Institute for Mental Health Research
Institute for Social Science Research
Nancy Eisenberg Junior Faculty Scholar Award
Arizona Department of Health Sciences (ADHS14-052688)
US Department of Health and Human Services and State of Arizona (ADHS Grant No. CTR057001)
National Institute on Aging (NIA) of the National Institutes of Health (NIH) (P30AG019610)
Arizona Alzheimer's Disease Research Center REC Fellows Program
Arizona Alzheimer's Consortium

Title: Fine motor deficits precede cognitive impairment and persist across the lifespan in the TgF344-AD rat model of Alzheimer's disease

Authors: *A. MELICK[1], K. CHRISTIANSEN[1], T. KRISHNAN[1], H. A. BIMONTE-NELSON[1], S. Y. SCHAEFER[2], S. C. BEEMAN[3], J. L. VERPEUT[1];
[1]Psychology, [2]Biomed. Engin., [3]Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ

Abstract: Alzheimer's disease (AD) is the most common cause of dementia and is characterized by accumulating amyloid beta plaques and tau neurofibrillary tangles that lead to progressive neurodegeneration and cognitive decline. Emerging staging frameworks indicate that pathology is detectable >15 years prior to clinical symptom onset, such that individuals are cognitively asymptomatic while still at risk for dementia (Bateman et al., 2012). This highlights the need for tools that detect disease-related changes before cognitive decline, when interventions are most effective.

Plasma biomarkers have improved the ability to identify early pathology. However, these measures do not predict future cognitive and functional decline. In conjunction with these biomarker tests, objective fine-motor skill assessments have been developed that predict both decline and dementia progression in individuals with mild cognitive impairment (Schaefer et al., 2025). Evidence suggests that fine motor impairments emerge prior to gross motor deficits during preclinical stages, meaning such an assessment may serve as a more sensitive indicator of early disease-related change. The current study aims to further investigate fine motor decline using a transgenic AD rodent model, capturing progression from disease onset through advanced stages.

The TgF344-AD (Tg, n=12) rat was assessed in a novel fine-motor apparatus (Melick et al., 2025) from 6 to 24 months of age and compared with age-matched, wildtype (Wt, n=12) controls. Cognition was evaluated in the Morris Water Maze (MWM), a test of spatial reference memory, with gross motor function tested using grip strength. Social LEAP Estimates Animal Poses (SLEAP) was used to examine fine motor behavior, including reach trajectory and task

strategy.
Tg rats exhibited impaired performance in the fine motor task across the lifespan, at 6 ($p < .001$), 12 ($p < .001$), 18 ($p = .0044$), and 24 ($p < .001$) months. In the MWM, Tg rats swam greater distances to the platform at 12 months ($p = .027$), indicating poorer performance that did not persist. Grip strength remained similar across ages. Tg rats showed significantly elevated plaque burden in hippocampal CA1 ($p = .0047$), motor cortex ($p < .001$), and cerebellar molecular layer ($p = .025$) compared to Wt at 10 months. Tg rats also had reduced pyramidal neuron dendritic complexity in the prelimbic cortex at 10 ($p = .002$) and 17 ($p < .001$) months.
Together, these findings suggest that functional fine motor decline may provide a more sensitive marker of AD-related dysfunction than conventional cognitive or gross motor measures, with the potential to detect disease-associated changes earlier in the progression of pathology.

Disclosures: A. Melick: None. **K. Christiansen:** None. **T. Krishnan:** None. **H.A. Bimonte-Nelson:** None. **S.Y. Schaefer:** None. **S.C. Beeman:** None. **J.L. Verpeut:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.12/T21

Topic:

Support: NIH Grant AG014449

Title: MicroRNA expression profiles in pretangle-bearing cholinergic basal forebrain neurons

Authors: J. S. BECK[1], B. MALONEY[2], E. J. MUFSON[3], D. K. LAHIRI[2], ***S. E. COUNTS**[1]; [1]Michigan State Univ., Grand Rapids, MI; [2]Indiana Univ., Indianapolis, IN; [3]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Cholinergic basal forebrain (CBF) projection neurons innervate the cortical mantle, mediating memory and attentional functions. CBF neurons are exquisitely prone to neurofibrillary tangle (NFT) formation during the prodromal stages of Alzheimer's disease (AD), leading to cholinergic neurodegeneration early in the disease process. However, the molecular mechanisms regulating the development of NFTs remain poorly understood. In this regard, small noncoding microRNAs (miRNAs) fill a major regulatory role in cellular expression patterns by binding target mRNAs and reducing protein translation. To test the extent to which miRNA dysregulation associates with early tau pathology, we used Nanostring nCounter Human miRNA Expression Panels to quantify ~800 miRNAs in CBF neurons isolated by laser-capture microdissection from basal forebrain tissue immunostained for the cholinergic-specific marker $p75^{NTR}$ and the well-established tau pretangle marker pS422. Basal forebrain tissue was obtained postmortem from Rush Religious Orders Study participants who displayed the full range of Braak stages upon neuropathological evaluation. To facilitate the collection of sufficient small RNA input for miRNA profiling, we harvested naïve CBF neurons from subjects displaying low

Braak stages (0-II) and pS422-bearing CBF neurons from subjects with higher Braak stages (III-V, *n* = 8/group). Six pooled samples of either $p75^{NTR}$+/pS422- or $p75^{NTR}$+/pS422+ CBF neurons were collected (~500 neurons/pool) for analysis. We identified 73 differentially expressed miRNAs (DEMs) in CBF neurons bearing pS422 pretangle pathology, including miR-7, miR-135a, miR-451a, and miR-575. The most high-confidence target mRNA/proteins predicted to be regulated by DEMs included: the dual-specificity phosphatase PTEN; anti-apoptotic BCL2; growth factor-related IGF1R and VEGFA; cell cycle regulators CDK2, CDK5R1, and CDK6; and endosomal trafficking regulators RAB5A and VAMP3. Pathway enrichment for target mRNAs included GO Biological Processes "regulation of cellular metabolic processes," "response to hypoxia," and "response to growth factors," suggesting that pS422 pathology-associated DEMs are operating in these pathways with specific functions in regulating mitochondrial function and growth factor signaling, as well as cell cycle kinase activity, cellular trafficking, and turnover. Ongoing studies include *in vitro* assessments to characterize the functional outcomes of validated DEM-target mRNA interactions and their implications for the development of pretangle tau pathology.

Disclosures: J.S. Beck: None. **B. Maloney:** None. **E.J. Mufson:** None. **D.K. Lahiri:** None. **S.E. Counts:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.13/T22

Topic:

Support: NIH Grant R21AG074539
NIH Grant R21AG076202
NIH Grant R56AG051086-06A1
NIH Grant 5P01AG014449-23 (26)

Title: Silencing REST by microRNA-153 Reduces Nestin and Increases Doublecortin Expression in Neural Stem Cells: Implications for Alzheimer's Disease and Autism

Authors: B. MALONEY[1], R. WANG[1], K. GREGERSON[1], D. SOKOL[2], K. NHO[3], J. ROGERS[4], N. GREIG[5], J. LONG[6], B. WOLOZIN[7], S. COUNTS[8], ***D. K. LAHIRI**[1,9]; [1]Dept. of Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Neurol., [3]Radiology & Imaging Sci., Indiana Univ. Sch. of Med., Indianapolis, IN; [4]Mass Gen Hosp Genet. & Age Res. Unit, Charlestown, MA; [5]Translational Gerontology Br., Natl. Inst. on Aging, NIH, Baltimore, MD; [6]Neurol., Washington Univ. Sch. of Med., St Louis, MO; [7]Pharmacol., Boston Univ. Schl Med., Boston, MA; [8]Transl Sci. & Mol Med, Family Med., Michigan State Univ., Grand Rapids, MI; [9]Indiana Alzheimer's Dis. Res. Ctr., Indianapolis, IN

Abstract: Neural stem cell (NSC) differentiation into neural progenitor cells and mature neurons is essential for normal brain development and maintenance. Its dysregulation contributes to neurodegenerative disorders, including Alzheimer's disease (AD) and autism spectrum disorder (ASD). However, molecular regulation of this process remains unclear. Circular RNAs and microRNAs (miRNAs or miR) may play critical roles therein. Among these, miR-153, miR-339, miR-346, and miR-298 have been implicated in regulating several proteins associated with AD pathology. Identifying factors that drive AD pathology and understanding how they regulate the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles are critical for developing novel therapeutic targets. Our research focuses on the regulation of amyloid-β precursor protein (APP), microtubule-associated protein tau (MAPT), α-synuclein (SNCA), and repressor element-1 silencing transcription factor (REST), a transcriptional repressor of neuronal genes that is dysregulated during AD. Although REST dysfunction has been linked to neurodegeneration, the mechanisms underlying its post-transcriptional regulation remain poorly understood. REST has also been implicated in ASD through regulating genes involved in neuronal development, synapse formation, and neural circuit function. We demonstrate that miR-153 directly targets the REST 3′-untranslated region (UTR), thereby reducing REST mRNA and protein levels in human cell lines. In addition, miR-153 suppressed APP and SNCA levels, suggesting coordinated regulation of multiple pathways of neurodegenerative diseases. Elevated miR-153 expression was associated with reduced AD risk, whereas increased REST expression correlated with a greater likelihood of disease. During neural differentiation, we observed that the effects of miR-153 were stage-dependent. In NSCs, miR-153 decreased REST and nestin-1 expression while increasing neuronal markers NSE and doublecortin, indicating promotion of neuronal differentiation and neurogenesis. Collectively, we identify miR-153 as a key regulator of REST and other neurodegeneration-associated genes. By coordinating suppression of APP, SNCA, and REST, miR-153 may reduce accumulation of toxic protein aggregates and promote neuronal differentiation. These results highlight the potential of miR-153 as both a biomarker and a therapeutic target for AD and ASD.

Disclosures: B. Maloney: None. **R. Wang:** None. **K. Gregerson:** None. **D. Sokol:** None. **K. Nho:** None. **J. Rogers:** None. **N. Greig:** None. **J. Long:** None. **B. Wolozin:** None. **S. Counts:** None. **D.K. Lahiri:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.14/T23

Topic:

Support: P01 AG014449
P30 AG066468
P50 AG005133
U19 AG068054

Title: Cortical cholinergic enzyme activity in adults with Down syndrome compared to clinical-pathological stages of Alzheimer's disease

Authors: *E. E. ABRAHAMSON[1,2], R. MARSDEN[3], N. ALRAQMANY[1], V. N. PIVTORAIKO[1], W. R. PALJUG[1], E. HEAD[3], E. J. MUFSON[4], M. D. IKONOMOVIC[1,2]; [1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Geriatric Res. Educ. and Clin. Ctr., Pittsburgh VA Healthcare Syst., Pittsburgh, PA; [3]Univ. of California, Irvine, CA; [4]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Cortical cholinergic enzyme activity loss is established in advanced Alzheimer's disease (AD) dementia. Whether similar deficits occur in adult Down syndrome individuals with AD pathology (DS+AD) is unknown. We measured choline acetyltransferase (ChAT) activity in postmortem frozen tissue homogenates from two Default Mode Network (DMN) hubs, frontal cortex (FC) and precuneus (PreC), from cases in the Rush Religious Order Study with last clinical diagnosis of no cognitive impairment (NCI) or mild AD (mAD), and ADRC patients with severe AD (sAD) and DS+AD from UPitt and UCI, respectively. NCI were divided into low- and high-pathology (LP-NCI, HP-NCI) groups. Soluble and insoluble (fibrillar) Aβ1-40 and Aβ1-42 ELISA and 3H-PiB binding were performed on the same samples assayed for ChAT activity. Sol-Aβ42 was significantly higher in DS+AD compared to all other groups, in both regions, while sAD had higher levels than mAD, HP-NCI, and LP-NCI in FC but not in PreC. Insol-Aβ42 was similar between DS+AD and sAD, with DS+AD having higher levels than mAD, HP-NCI, and LP-NCI in both regions, and sAD having higher levels than LP-NCI in FC and LP-NCI and HP-NCI in PreC. In both regions, Sol- and Insol-Aβ40 were significantly higher in DS+AD compared to all other groups, with sAD>mAD>HP-NCI>LP-NCI. 3H-PiB binding in both DS+AD and sAD was significantly higher than in LP-NCI and HP-NCI, but not mAD, in FC. In PreC, 3H-PiB binding in sAD was higher than DS+AD, HP-NCI, and LP-NCI. In both regions, ChAT activity was significantly lower in DS+AD and sAD compared to other groups which were similar in FC but had a significant stepwise decrease LP-NCI>HP-NCI>mAD in PreC. ChAT activity in DS+AD was similar to sAD in PreC but significantly higher than sAD in FC. Across all groups, lower ChAT activity correlated significantly with greater soluble and insoluble Aβ42 and Aβ40, and greater 3H-PiB binding, in both regions. Cortical ChAT activity impairs with greater Aβ burden across clinical-pathological stages of AD and in DS+AD. However, despite significant Aβ burden, HP-NCI and mAD show stable ChAT activity in FC, but not PreC. DS+AD also have better preserved ChAT activity than sAD in FC, but not in PreC. The mechanism/s underlying cholinergic plasticity changes in FC and vulnerability of PreC cortex remain to be elucidated in both AD and DS+AD.

Disclosures: E.E. Abrahamson: None. **R. Marsden:** None. **N. Alraqmany:** None. **V.N. Pivtoraiko:** None. **W.R. Paljug:** None. **E. Head:** None. **E.J. Mufson:** None. **M.D. Ikonomovic:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.15/T24

Topic:

Support: Edson Initiative Seed Grant

Title: Effect of Short-term Estradiol on Choline Metabolism Across Brain and Peripheral Tissues Following Ovariectomy-Induced Estrogen Depletion

Authors: *J. M. JUDD[1,3], W. WINSLOW[3], A. V. PRAKAPENKA[4], R. VELAZQUEZ, Jr.[5,2]; [2]Sch. of Life Sci., [1]Arizona State Univ., Tempe, AZ; [3]ASU-Banner Neurodegenerative Res. Ctr., Biodesign Inst., Tempe, AZ; [4]Biomed. Sci., Midwestern Univ., Downers Grove, IL; [5]Neurodegenerative Dis. Res. Ctr., ASU Biodesign Inst., Tempe, AZ

Abstract: Around age 51 women undergo menopause, the cessation of menses for a year due to ovarian depletion. Notably, ~250,000 women annually undergo bilateral oophorectomy, surgical ovarian removal, causing abrupt menopause onset. Both natural and surgical menopause exhibit a substantial reduction in estrogen, increasing dementia risk, through Amyloid-β buildup, neuroinflammation, and metabolic dysfunction. Estrogen activates the liver enzyme phosphatidylethanolamine N-methyltransferase (PEMT), which produces ~30% of the required choline, an essential molecule that is critical for liver and brain function, and reduces inflammation, liver disease, and metabolic dysfunction. The remaining 70% of necessary choline comes from diet. Higher choline intake is vital for brain health across the lifespan and protective against cognitive decline, reducing dementia risk. Dementia patients exhibit lower serum choline. Alarmingly, only 11% of Americans achieve adequate intake. Since estrogen activates PEMT, following low choline intake, premenopausal women are protected against liver disease but postmenopausal women, with diminished estrogen, are at increased risk of liver pathology. Given the overlap with dementia risk, metabolic imbalances, and inflammation following choline deficiency or menopausal status, understanding shared mechanisms could inform interventions to prevent or delay dementia in women. Here, three-month-old female Sprague Dawley rats underwent ovariectomy (ovx). Vaginal smears for 6 days confirmed acyclicity, a menopause-like state. Three weeks after ovx, rats were given 0.1, 3, or 10 µg of Estradiol (E2), or sesame oil vehicle via subcutaneous injection for 2 days. All rats were fed standard chow with adequate choline (1.2g/kg). Serum and frontal cortical (FC) choline, cytokine, PEMT, serum E2, and FC estrogen receptor-α (ER-α) levels did not differ between groups, likely due to the short duration of E2 injection. However, insightful correlations were observed. FC ER-α positively correlated with PEMT levels, reflecting the importance of estrogen on regulating both ER-α and PEMT levels. A trending negative correlation revealed that PEMT levels increased with lower E2, suggesting a compensatory upregulation in PEMT. Higher serum E2 was correlated with lower FC choline, which may indicate increased choline utilization rather than reduced availability; E2 promotes neuronal plasticity and membrane remodeling, processes that require choline-containing phospholipids. These data provide evidence for a relationship between estrogen signaling and choline metabolism, which should be further studied with longer E2 treatment.

Disclosures: J.M. Judd: None. **W. Winslow:** None. **A.V. Prakapenka:** None. **R. Velazquez:** None.

Poster

PSTR302: Alzheimer's Disease:?Pathological and Reverse Translational Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR302.16/T25

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

Support: National Key Research and Development (R&D) Program of China (2021YFA0805100)
Key Program of the National Natural Science Foundation of China (32530027)
National Science and Technology Innovation 2030 Major Program (2021ZD0204400)

Title: Spatial reconstruction of vascular-centered neurovascular unit decodes microenvironmental remodeling in the human Alzheimer’s disease brain

Authors: *Y. HE[1], L. WANG[2];
[1]Univ. of Chinese Acad. of Sci., Hangzhou, China; [2]BGI research, Hangzhou, China

Abstract: Alzheimer's disease (AD) involves complex multicellular cascades within the neurovascular unit (NVU). While spatial transcriptomics can capture cells in situ, quantitative modeling of continuous microenvironmental network collapse-rather than isolated shifts in cell abundance-remains a major computational challenge. Utilizing Stereo-seq datasets spanning 44 tissue chips from 28 individuals, we established a digital NVU model anchored around three biological constraints: each candidate unit was anchored by a deconvolved endothelial and mural-cell vascular field, retained only when the vascular core was embedded in a local neuron-astrocyte-vascular neighborhood, and supported by ligand-receptor communication evidence. We reveal that AD-associated NVU disruption is highly selective and partitions into distinct hippocampal and cortical programs. In the hippocampus, FAS, SLRM and CA1 subregions showed elevated NVU density and vascular-cell remodeling, with FAS and SLRM emerging as the most vulnerable subregions. These hippocampal NVUs were marked by disease-associated astrocyte and microglial enrichment, AD-elevated immune and vascular-development modules, and heightened microglia-centered immune-vascular signaling, including SPP1-CD44, APP-CD74, CLU-TREM2_TYROBP and ANGPTL4-ITGAV_ITGB3 interactions. In contrast, the prefrontal cortex showed layer-specific remodeling concentrated in L23 and L456, but with a divergent communication landscape: L23 exhibited reduced mean communication strength, whereas ANGPTL4-SDC4 signaling remained concentrated around endothelial cells. By registering amyloid-β pathology, we demonstrate that plaque proximity intensifies NVU remodeling, increasing NVU density, reactive-glial accumulation and ligand-receptor activity while driving a conserved 128-gene stress signature linked to mitochondrial dysfunction, apoptosis and angiogenesis. Finally, a hierarchical graph neural network (HGNN) integrated multiscale NVU features and prioritized regional vulnerability and ligand-receptor communication above cell-type abundance alone. Together, our findings define AD pathogenesis as a regionally patterned neural-immune-vascular process and provide an interpretable spatial framework for decoding hippocampal and cortical tissue vulnerability in human neurodegeneration.

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

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.01/T26

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

Support: This work is supported by a grant from the National Institute on Aging (R01AG075440 1RF1AG074256 to A.K.S.)

Title: Extracellular Vesicles from hiPSC-derived NSCs Can Rewire Neuroinflammatory and Neurodegenerative Programs in Microglia and Astrocytes in an Alzheimer's Model

Authors: *M. GUPTA[1,2], L. N. MADHU[2], M. KODALI[2], A. K. SHETTY[2];
[1]Texas A&M Univ., College Station, TX; [2]Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Texas A&M Univ. Naresh Vashist Col. of Med., College Station, TX

Abstract: Extracellular vesicles from human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSC-EVs) exhibit anti-inflammatory properties and thus hold promise for slowing the progression of Alzheimer's disease (AD). This study investigated the effects of intranasal administration of hiPSC-NSC-EVs (two doses of 30×10^9 EVs separated by 2 weeks) on microglia, astrocytes, and macrophages in 3-month-old 5xFAD mice using single-cell RNA sequencing. Analytical tools (Seurat, destiny, slingshot, and liana) were used to examine cell heterogeneity, trajectories, and intercellular communication at 72 hours after the second EV dose. Cells were grouped by canonical markers and compared across naive, AD-vehicle, and AD-EVs groups. Sub-clustering revealed about 10 microglial, 6 astrocyte, and 6 macrophage subtypes. Pseudotime analysis using Slingshot and Destiny on uniform manifold approximation and projection embeddings delineated a trajectory from homeostatic to disease-associated states across all three cell types. Spearman correlation analyses of gene expression with diffusion component 1 revealed distinct patterns along these trajectories in these cells. Microglial trajectory analysis indicated that hiPSC-NSC-EVs treatment may rebalance or remodel microglial responses toward less inflammatory phenotypes, with inhibition of transforming growth factor-β, AD, and vascular endothelial growth factor signaling pathways, and upregulation of cholecystokinin receptor, apoptosis, and nicotinic acetylcholine signaling pathways. In astrocytes, EVs treatment promoted progressive transition toward reactive neurovascular and synaptic remodeling. Macrophages also shifted toward homeostasis, with increased major histocompatibility complex 1 antigen-presenting activity and G-protein protein-coupled receptor signaling after treatment. Overall, hiPSC-NSC-EVs led to coordinated remodeling of microglia, astrocytes, and macrophages in AD mice. Notably, EVs treatment slowed progression to terminal stress-related states while preserving naïve-like signatures, suggesting that EVs can modulate microglial and astrocytic state transitions in the disease microenvironment. EVs also reduced pro-inflammatory and neurodegeneration-related

intercellular signals (e.g., *S100A8*/*A9-TLR4*, *S100A8*/*A9-ITGB2*, *APP*) and restored apolipoprotein E-focused pathways involved in homeostasis and repair. Thus, intranasal treatment with hiPSC-NSC-EVs can promote a shift in microglial, astrocytic, and macrophage phenotypes toward homeostatic and repair-like states, highlighting their potential to restrain AD progression.

Disclosures: M. Gupta: None. **L.N. Madhu:** None. **M. Kodali:** None. **A.K. Shetty:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.02/T27

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

Support: Grant from the National Institutes for Aging (R01AG075440 1RF1AG074256 to A.K.S.)

Title: Long-term effects of intranasal administrations of extracellular vesicles from hiPSC-derived NSCs on cognitive function and tau phosphorylation in PS19 model of tauopathy

Authors: *R. S. BABU, L. N. MADHU, C. FAN, B. SHUAI, X. RAO, C. HUARD, S. VENKATA GANESH, P. TARALE, M. KODALI, A. K. SHETTY;
Texas A&M Univ., College Station, TX

Abstract: Tauopathies are neurodegenerative diseases characterized by increased intraneuronal tau phosphorylation, leading to neurofibrillary tangles that induce neuroinflammation, progressive neuronal loss, and cognitive decline. Extracellular Vesicles (EVs) released by human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSC EVs) carry various miRNAs and proteins with therapeutic benefits, including inhibition of tau phosphorylation, neuroprotective effects, and anti-inflammatory effects. This study investigated the effects of intermittent intranasal administrations of relatively low doses of hiPSC-NSC EVs (~15 billion/dose) in PS19 mice. Male and female PS19 mice received hiPSC-NSC-EVs at 4, 5, 6, and 7 months of age, followed by neurobehavioral tests to evaluate pattern separation, object location memory, and recognition memory. The animals were euthanized for brain tissue analysis at 8.5 months of age. Compared to male and female naïve mice, both male and female PS19 mice receiving vehicle displayed impaired performance in a pattern separation task. In contrast, male and female PS19 mice treated with hiPSC-NSC-EVs showed improved performance in the pattern separation task. In the object location memory task, vehicle-treated male and female PS19 mice showed impairments, which were improved only in female PS19 mice receiving hiPSC-NSC-EVs. However, in the novel object recognition memory task, both male and female PS19 mice receiving vehicle or hiPSC-NSC-EVs showed impairments compared to their naive control counterparts. Analysis of tau phosphorylation using the AT8 ELISA revealed significantly increased tau phosphorylation in both the hippocampus and the frontal cortex of

male and female PS19 mice treated with vehicle. The extent of tau phosphorylation in male and female PS19 mice receiving hiPSC-NSC-EVs treatment was reduced but did not differ statistically from either the naive control or the vehicle-treated PS19 groups, implying a partial reduction in tau phosphorylation with EVs treatment. Analysis of GFAP+ area fractions in the hippocampus revealed no differences across the three female groups. Analyses in male groups and quantification of GFAP+ astrocytes and IBA-1+ microglia are currently in progress. The results reveal that intermittent low-dose administrations of hiPSC-NSC-EVs can maintain better pattern separation function and partially reduce tau phosphorylation in both sexes, but are insufficient to prevent declines in additional cognitive domains during the advanced stage of the disease, suggesting that higher doses of hiPSC-NSC-EVs may be required to enhance their therapeutic efficacy.

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Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.03/T28

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

Support: This work is supported by a grant from the National Institutes for Aging (R01AG075440 1RF1AG074256 to A.K.S.)

Title: Long-term Intermittent Fasting Regimen Alleviates Cognitive Decline, Neuroinflammation, and Microbiome Alterations in an Alzheimer's Disease Mouse Model

Authors: *L. N. MADHU, Y. SOMAYAJI, H. HERNANDEZ, B. SHUAI, M. GUPTA, M. KODALI, A. K. SHETTY;
Inst. For Regen Med, Texas A&M Univ. Coll Med., College Station, TX

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by the deterioration of cognitive and memory function. Key pathological features of AD include neuroinflammation, extracellular accumulation of amyloid-beta plaques, hyperphosphorylation of tau in neurons, and adverse changes in the gut microbiome. Intermittent fasting (IF) is a dietary intervention that has demonstrated health benefits across generations. This study investigated the effects of a long-term 16:8 IF regimen on pathogenesis in 5xFAD mice. One-month-old female 5xFAD mice were randomly assigned to either a non-fasting (NF) group or an IF group, alongside age-matched naïve controls. Mice in the IF group underwent daily cycles of 16 hours of food deprivation followed by 8 hours of ad libitum feeding. At 11 to 12 months of age, cognitive and mood functions were assessed. Mice subjected to long-term IF exhibited improved ability for object location memory, pattern separation, and temporal pattern processing

tasks, and displayed reduced anxiety and depressive-like behaviors compared with the NF group. Brain tissue analysis at 12 months of age revealed that long-term IF reduced amyloid plaque load, Aβ-42 levels, microglial clustering, the proportion of microglia expressing NLRP3 inflammasome complexes, and NLRP3-p38/MAPK activation in the hippocampus relative to the NF group. Additionally, long-term IF decreased mTOR signaling and increased levels of autophagy-related proteins, including beclin1 and ATG5, while reducing p62 accumulation in hippocampal neurons. IF also maintained better hippocampal neurogenesis, evidenced by higher numbers of newly born doublecortin-positive neurons in the subgranular zone-granular cell layer. Furthermore, 16S rRNA gene amplicon sequencing of fecal samples revealed that Lactobacillus taxa were more abundant in the AD-IF group, whereas Bacteroides, Alistipes, and Rikenellaceae predominated in the AD-NF group, implying that long-term IF promoted the maintenance of distinct and potentially beneficial fecal microbiome communities in 5xFAD mice. Thus, a long-term 16:8 intermittent fasting regimen in 5xFAD mice not only preserves better cognitive and mood function for up to 12 months of age but also significantly reduces neuroinflammatory signaling and amyloid plaque burden, boosts hippocampal neurogenesis, and mitigates adverse changes in the gut microbiome, all of which are likely beneficial for neuroprotection against AD-associated neurodegeneration.

Disclosures: L.N. Madhu: None. **Y. Somayaji:** None. **H. hernandez:** None. **B. Shuai:** None. **M. Gupta:** None. **M. Kodali:** None. **A.K. Shetty:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.04/T29

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

Support: National Institutes for Aging (R01AG075440 1RF1AG074256 to A.K.S.)

Title: Permethrin Exposure Accelerates Cognitive Decline and Neuropathological Changes in the 5xFAD Mouse Model of Alzheimer’s Disease

Authors: *H. A. AHMED, L. N. MADHU, Y. SOMAYAJI, A. CHOPRA, B. SHUAI, X. RAO, A. K. SHETTY;
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Abstract: Alzheimer’s disease (AD) is the leading cause of dementia globally and is characterized by extracellular amyloid-beta (Aβ) plaque buildup, increased oxidative stress, neuroinflammation, and tau phosphorylation, all of which likely contribute to progressive cognitive decline. Environmental factors, such as pesticide exposure, may influence disease progression in populations with a genetic predisposition. Permethrin (PM), a commonly used pyrethroid insecticide, has been shown to impair hippocampal and cortical function with long-

term exposure; however, its role in AD pathogenesis among genetically susceptible individuals remains unclear. The present study examined whether short-term dermal exposure to PM exacerbates AD-related neuropathology in the 5xFAD mouse model, which recapitulates amyloidosis and familial AD. Male 5xFAD and wild-type (WT) mice were divided into four groups: WT-Veh, WT-PM, AD-Veh, and AD-PM. Starting at 1.5 months of age, mice received daily dermal applications of vehicle or PM (0.6 mg/kg) for 10 consecutive days. At 3 to 4 months of age, neurobehavioral tests were conducted to assess cognitive function, and all mice were euthanized at 4 months of age. Hippocampal and cortical tissues were analyzed by immunohistochemistry to evaluate amyloid-beta plaque deposition, microglial activation, and astrocyte hypertrophy. Oxidative stress was assessed by quantifying malondialdehyde (MDA) and protein carbonyl concentrations. Mice in the AD-PM group demonstrated cognitive impairments in object location, object-in-place, and novel object recognition tasks, while all other groups remained unimpaired. Relative to the AD-Veh group, AD-PM mice exhibited significantly increased Aβ plaque burden, enhanced microglial clustering, and elevated levels of GFAP-positive astrocyte elements in the hippocampus, entorhinal cortex, and amygdala. Furthermore, AD-PM mice showed higher concentrations of MDA, a marker of lipid peroxidation, and protein carbonyls, a marker of protein oxidation, indicating elevated oxidative stress. These results indicate that PM exposure accelerates cognitive deficits, amyloid plaque accumulation, neuroinflammation, and oxidative stress in 5xFAD mice, suggesting that environmental pesticide exposure accelerates AD progression in genetically susceptible populations. This study underscores the need to elucidate environmental contributions to AD pathogenesis and to develop preventive strategies for at-risk individuals.

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Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.05/T30

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

Support: Centre For Brain Research core grant
DBT Fellowship Award- DBTHRDPMU/JRF/BET-22/I/2022-23/03

Title: Dysregulation of Peroxiredoxin-V in Alzheimer’s disease

Authors: *A. GUPTA[1,2], R. KOMMADDI[1];
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Abstract: Peroxiredoxin-V (PrxV) is a crucial antioxidant enzyme abundantly expressed in neurons, where it plays an important role in maintaining redox homeostasis by scavenging

reactive oxygen species (ROS), particularly H_2O_2. Although oxidative stress is widely recognized as a key contributor to the pathogenesis of Alzheimer's disease (AD), the role of PrxV in AD-associated neurodegeneration remains poorly understood. Therefore, this study aimed to investigate alterations in PrxV expression and its contribution to oxidative stress during AD progression. To address this, we utilized the APP/PS1 mice at 1, 3, and 9 months of age. Initially, ROS levels and PrxV expression were evaluated in brain tissues as well as in primary neurons derived from these mice. ROS measurements revealed significantly elevated ROS levels in cortical and hippocampal brain lysates from APP/PS1 mice compared with wild-type controls. Consistently, primary cortical neurons derived from APP/PS1 mice also exhibited increased ROS accumulation, indicating enhanced oxidative stress in the AD brain. Notably, PrxV expression was markedly reduced in APP/PS1 mice brain tissues, as well as in primary cortical neurons derived from APP/PS1 mice, suggesting that PrxV dysregulation may contribute to AD associated disease progression. Collectively, these findings demonstrate that PrxV expression is dysregulated in the AD brain and that reduced PrxV levels are associated with elevated oxidative stress. Thus, PrxV may represent a potential therapeutic target for mitigating oxidative stress-related pathology in Alzheimer's disease.

Disclosures: A. Gupta: None. **R. Kommaddi:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.06/T31

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

Support: NIH T32NS082145
NIH P30AG066546
NIH P30AG072978
NIH U01NS086659
NIH U54NS115266

Title: Microglial sensome landscapes across tauopathies

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Abstract: Background: Microglia detect and respond to chemotactic cues in neurodegenerative diseases. The *microglial sensome*, a defined set of genes, enables microglia to sense changes in brain parenchyma. In Alzheimer's disease (AD), "homeostatic" sensome genes are downregulated and "responsive" sensome genes are upregulated. However, it is unclear how the

microglial sensome is altered in other tauopathies including chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). We hypothesize that the microglial sensome protein landscape in CTE, CBD, and PSP individually differ from AD.
Methods: To characterize the microglial sensome, serial sections of formalin-fixed, paraffin-embedded brain tissue from frontal neocortex of decedents with pathologically confirmed AD (n= 13), CTE (n= 14), CBD (n= 9), and PSP (n= 11) were labeled with antibodies against sensome proteins, phosphorylated tau, and phosphorylated neurofilament. Labeled tissue was digitized and analyzed using Leica Aperio AT2 Slide Scanner and Imagescope software. Total percent positive staining was averaged for grey and white matter regions. Microglia morphology was characterized via ImageJ FIJI skeletonize plugin. Whole slide images were processed for cell segmentation via deep-learning U-net model and analyzed with Genentech's Spatial Quantitative Pathology Features (SpatialQPFs) R package. Additionally, to assess translatability of the microglial sensome in tauopathies, an *in vivo* mouse model of neurodegeneration was used to assess active changes in microglia function and activity in the context of tau pathology.
Result: We characterized microglial landscapes using SpatialQPFs, highlighting sensome differences that may contribute to the disease microenvironment. Principle component analysis reveal grouping of microglial markers by functional state (i.e. homeostatic markers vs. responsive markers) as well as by tau pathology and antigen presentation. Lower IBA1 and P2RY12 levels were observed in CTE compared to PSP grey matter and lower CD68 levels in CBD white matter. Differences in cell body morphology were observed between AD and CTE grey matter for IBA1- positive microglia.
Conclusion: These findings suggest neurodegenerative pathology associated with each disease may elicit distinct microglial adaptations contributing to divergent neurodegenerative pathways. Future work will explore the therapeutic potential of altering microglial sensome proteins in a disease model to assess changes to disease progression.

Disclosures: T. Adetona: None. **S.C. Hopp:** None. **S. Smith:** None. **M.E. Flanagan:** None. **T.D. Stein:** None. **A.C. McKee:** None. **D.W. Dickson:** None. **K.F. Bieniek:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.07/T32

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

Support: University of Rochester Aging and Alzheimer's Disease Training Program (UR-AADTP) grant (T32 AG076455

Title: AAV-P301L-Tau Induces Progressive Tau Hyperphosphorylation and Neuroinflammation in the Dorsal Hippocampus.

Authors: *T. ONI[1], K. WANG[2], M. O'BANION[3];
[1]Cellular/Molecular Pharmacol. & Physiol., Univ. of Rochester Sch. of Med. & Dent., Rochester, NY; [2]Neuroscience, Cell. Mol. Pharmacol. & Physiol., [3]Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Tauopathies are characterized by pathological tau accumulation, spread, and neuroinflammation. Traditional transgenic tauopathy models are limited by developmental-onset and widespread tau expression, restricting their ability to capture the progressive and region-specific nature of tau pathology in Alzheimer's disease (AD). To address this, we used an adeno-associated viral vector carrying human P301L-tau (AAV-huTau) to induce tauopathy in C57BL/6 mice with spatial and temporal precision. This model enables controlled tau propagation and targeted testing of therapeutic interventions. A key therapeutic target is cyclooxygenase-2 (COX-2), an inflammatory enzyme upregulated in AD. COX-2 metabolizes arachidonic acid into pro-inflammatory prostaglandins, including PGE2, and can also convert the anti-inflammatory endocannabinoid anandamide into prostaglandin precursors, potentially exacerbating inflammation. We injected 3-month-old C57BL/6 mice unilaterally in the dorsal hippocampus with AAV-huTau or AAV-GFP and confirmed hyperphosphorylation of Tau (pTau) in the ipsilateral hippocampus of AAV-huTau-injected mice, which was absent in AAV-GFP controls. pTau levels were strongly correlated with viral huTau expression. We also observed huTau spread to the contralateral CA4 region. Additionally, increased CD68+ and Iba1+ immunoreactivity in the ipsilateral hippocampus of AAV-huTau mice indicated robust microglial inflammatory response. Sustained huTau and pTau expression was confirmed in affected hippocampal regions, including ipsilateral CA1 and dentate gyrus at 2 and 4 weeks post injection. Furthermore, pTau+ and Iba1+ expression were significantly increased at 10 weeks compared to earlier time points, consistent with progressive pathological accumulation and neuroinflammatory responses. Overall, this model provides a precise and experimentally tractable platform to study tau progression and evaluate anti-inflammatory therapies targeting COX-2 and related prostaglandin-endocannabinoid signaling pathways.

Disclosures: T. oni: None. **K. Wang:** None. **M. O'Banion:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.08/U1

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

Support: NIH Grant R35NS132150
NIH Grant R01NS096748
NIH Grant R01NS109670
Conrad N. Hilton Foundation Grant #17734
Conrad N. Hilton Foundation Grant #18394

Title: Sex Differences in Aβ42-associated Microglial Engulfment in Alzheimer's Disease Model

Authors: ***M. SMITH**[1], N. ITOH[1], S. WENDIN[1], R. VOSKUHL[2];
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Abstract: Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) accumulation, neuroinflammation, and progressive cognitive decline, with biological sex influencing disease risk and trajectory. Microglia play a central role in Aβ clearance; however, whether sex-dependent differences in microglia-Aβ interactions occur at early ages remains unclear. Using the AppNL-F mouse model for AD, we examined male and female AppNL-F and wild-type (WT) mice at young (3 months) and midlife (12 months) ages to assess age and sex-dependent disease effects. Cognitive testing was done using Morris Water Maze behavioral testing. Hippocampal CA1 and dentate gyrus (DG) regions were immunostained for ionized calcium-binding adaptor molecule 1 (IBA1), cluster of differentiation 68 (CD68), triggering receptor expressed on myeloid cells 2 (TREM2), and amyloid beta 42 (Aβ42) to assess microglial activation and Aβ pathology. Results of Morris Water Maze showed that AppNL-F females were cognitively intact at midlife, whereas midlife AppNL-F males showed a cognitive deficit. Further, AppNL-F males at midlife displayed significantly increased levels of Aβ42 as compared to age-matched controls. In contrast, midlife female AppNL-F females did not show increased Aβ42 as compared to WT females. Additionally, at young age, AppNL-F males showed decreased $IBA1^{+}CD68^{+}$ and $IBA1^{+}TREM2^{+}$ area fractions relative to WT males, while young AppNL-F females did not show these decreases when compared to their WT counterparts. These findings suggest that females may maintain a more protective microglial response during early AD stages, which could contribute to sex differences in downstream disease trajectories. To investigate mechanisms underlying female resilience during disease, female AppNL-F mice with selective deletion of estrogen receptor (ER) β in neurons and WT controls were evaluated at young (3 months), midlife (12 months), and old (18 months) ages. Morris Water Maze testing demonstrated that female ERβ cKO mice exhibited cognitive deficits at midlife. In the hippocampal CA1 region, ERβ cKO mice at old age showed increased $Aβ42^{+}$ area fraction compared to ERβ WT mice at old age. Notably, young and midlife ERβ cKO mice had reduced $IBA1^{+}CD68^{+}$ and $IBA1^{+}TREM2^{+}$ microglia compared to ERβ WT mice. Together, these findings implicate neuronal ERβ in preserving microglial activity, providing a potential mechanism for female resilience against AD pathology before estrogen loss with menopause.

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Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.09/U2

Topic: B.09. Glial Mechanisms

Title: Disease-associated CD63 regulates microglial tau clearance and spreading in tauopathy

Authors: *J. HACKER;
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Abstract: In tauopathies, accumulation and spread of hyperphosphorylated tau correlates with progressive neurodegeneration and cognitive decline. Microglia maintain brain homeostasis by clearing tau aggregates through phagocytosis and lysosomal degradation; however, when lysosomal degradation is compromised in disease, microglia alternatively clear tau by releasing tau-containing exosomes, facilitating tau propagation. Transcriptomic analyses of tauopathy mouse models identify CD63, a regulator of both exosome release and protein clearance via the endolysosomal network (ELN), as one of the most significantly upregulated genes in disease-associated microglia (DAM). We hypothesize that CD63 regulates microglial ELN-mediated tau clearance via lysosome-mediated degradation and exosome-mediated release, thus impacting tau pathology. To examine CD63's role in microglia tau clearance via the lysosome, we utilized *in vitro* immunocytochemistry and live-cell pH-sensitive LysoSensor assays of CD63-knockout primary mouse microglia to show that CD63 deletion impairs microglia phagolysosome acidification and reduces microglia lysosomal degradation of tau aggregates compared to control. Nanoparticle tracking analysis of microglia-secreted exosomes indicates CD63-/- microglia release more exosomes compared to control; quantification of exosomal tau is ongoing. To examine how CD63-dependent changes in lysosome/exosome mediated tau clearance affect tau pathology, we utilized immunofluorescence and single-cell RNA-sequencing (scRNA-seq) of CD63-/- PS19 tauopathy mice. Immunofluorescence revealed CD63-/- PS19 mice have fewer phosphorylated tau aggregates, reduced microgliosis, and attenuated hippocampal atrophy relative to PS19 controls. scRNA-seq analysis of CD63-/- PS19 hippocampal tissue is ongoing to characterize CD63-dependent transcriptomic alterations in microglial ELN pathways that may contribute to alterations in tau pathology *in vivo*. These findings establish CD63 as a key regulator of microglial tau processing and tau pathology in the PS19 mouse model. Further characterization of CD63's role in microglial clearance of tau aggregates may identify therapeutic targets aimed at slowing tau pathology, neurodegeneration, and cognitive decline in patients with tauopathies.

Disclosures: J. Hacker: None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.10/U3

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

Support: Ministerio de Ciencia e Innovación (PID2021-125785OA-I00)
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Alzheimer Association (AARG-22-968879)

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FPI Grant (PRE2022-102708)

Title: Stage-dependent modulation of microglial ADP receptor signaling shapes tau-associated neurodegeneration in APP/Tau mice

Authors: ***Y. JIN**[1,2], U. FRAGA BOUZAS[1,2], I. PALLÁS[1,2], M. MOR-GIMENO[1,2], C. A. SAURA[3], M. PUIGDELLIVOL CAÑADELL[1,2];
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Abstract: Tau pathology is closely associated with cognitive decline in Alzheimer's disease (AD), yet the mechanisms linking tau accumulation to neuronal dysfunction and neurodegeneration remain incompletely understood. Microglia are increasingly recognized as dynamic modulators of AD progression, but their contribution may vary across disease stages and pathological contexts. Here, we tested whether pharmacological inhibition of microglial ADP receptor signaling modulates tau-associated functional and histopathological alterations in APP/Tau mice, and whether comparable effects are observed in single-transgenic Tau mice. APP/Tau mice were treated with an ADP receptor inhibitor during either an early or mild-advanced disease stage. In this model, ADP receptor inhibition was associated with preserved spatial memory across both treatment windows. Early intervention attenuated hippocampal tau-associated pathology and preserved markers of circuit integrity, suggesting protection from early disease-related disruption. At a mild-advanced stage, treatment did not substantially reduce established tau burden but was associated with partial preservation of hippocampal neuronal integrity and a shift in microglial reactivity toward a less reactive profile. To assess whether these effects reflected a general modulation of tau-driven pathology, single-transgenic Tau mice were also treated and evaluated. As tau pathology emerges later in this model, these mice received an extended treatment regimen covering the period of tau pathology development. Despite this prolonged intervention, comparable behavioral and histopathological benefits were not observed, suggesting that the protective response seen in APP/Tau mice may depend on an amyloid-accelerated pathological environment. Together, these findings suggest that microglial ADP receptor signaling modulates tau-associated neurodegeneration in a stage- and pathology-context-dependent manner. Rather than exerting a uniform anti-tau effect, ADP receptor inhibition may limit early tau-associated pathology while partially dissociating established tau burden from downstream neuronal loss in APP/Tau mice. Overall, our results position microglial ADP receptor signaling as a stage-sensitive checkpoint in amyloid-tau-microglia interactions, highlighting this pathway as a promising modulator of AD-related neurodegeneration.

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Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.11/U4

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

Support: T32 ES033955/ES/NIEHS NIH HHS/United States

Title: Differential Microglial TSPO Response to Amyloid-β and Tau Pathology in Alzheimer's Disease

Authors: *D. A. MARTINEZ-PEREZ[1,2], J. L. MCGLOTHAN DZIEDZIC[2], A. N. RODICHKIN[2], Z. BURSAC[3], A. VILLEGAS-LANAU[4], T. R. GUILARTE[2];
[1]Florida Intl. Univ., Miami, FL; [2]Envrn. Hlth. Sci., [3]Dept. of Biostatistics, Robert Stempel Col. of Publ. Hlth. & Social Work Florida Intl. Univ., Miami, FL; [4]Group of Neurosciences of Antioquia, Univ. of Antioquia, Medellin, Colombia

Abstract: Translocator protein 18 kDa (TSPO) positron emission tomography (PET) imaging is widely used to assess neuroinflammation in Alzheimer's disease (AD). However, the interpretation of increased TSPO signal remains limited due to insufficient understanding of the cellular sources and its relationship to amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). AD can be categorized into familial early-onset AD (fEOAD), sporadic early-onset AD (sEOAD), and sporadic late-onset AD (sLOAD) cases. In this study, TSPO levels were quantified in postmortem brain tissue from male and female control, sLOAD, sEOAD, and fEOAD subjects. Quantitative TSPO autoradiography revealed significantly elevated TSPO levels in the frontal cortex of AD cases compared to controls, with the highest increase observed in fEOAD cases. To identify the cellular sources of TSPO, high-resolution immunofluorescence confocal microscopy using nanobodies combined with 3D-rendering and Imaris-based image analysis was employed. The results demonstrate that the increased TSPO signal was predominantly associated with microglia rather than astrocytes. Both microglial cell number and TSPO volume per microglial were increased in AD. Notably, microglial density declined with increasing brain age in AD cases. Further analyses revealed that increased TSPO expression was primarily driven by microglia localized to neuritic plaques. Advanced imaging also enabled the visualization of Aβ plaque fragment engulfment by microglia exhibiting high TSPO expression. In contrast, although microglia were frequently observed near phosphorylated tau (p-tau) pathology, no evidence of p-tau uptake or engulfment by microglia was observed. Consistent with these findings, microglial TSPO expression was significantly increased in the cerebral cortex of AD subjects, particularly in microglia associated with amyloid aggregates and neuritic plaques. The selective presence of Aβ fragments, but not p-tau, within high-TSPO content microglia suggests functionally distinct microglial responses to Aβ and tau pathologies. Additionally, image analyses identified neuronal cell bodies with various degrees of Aβ and tau aggregation suggesting a transition from Aβ to tau pathology within the same neuronal cell body that does not appear to depend on microglial activity. Collectively, these findings support the interpretation that elevated TSPO levels reflect a neuroinflammatory response linked to microglial engagement with Aβ plaques. This process may contribute to AD progression and highlights TSPO as a potential target for TSPO ligand-based therapy.

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Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.12/U5

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

Support: MICIU/AEI/10.13039/501100011033 and FEDER Una manera de hacer Europa Grant PID2021-125785OA-I00
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by MICIU/AEI/10.13039/501100011033 and by ESF+ FPI Grant PRE2022-102708
FI Grant 2024 FI-1 00935

Title: Microglial ADP receptor blockade exerts stage-dependent effects on neuroimmune dysfunction in APP/Tau mice

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Abstract: Microglial are key regulators of brain homeostasis, synaptic function and neuronal network activity. In Alzheimer's disease (AD), disruption of microglia-neuron communication may contribute to progressive neurodegeneration and cognitive decline. Purinergic signalling is a central mechanism by which microglia detect neuronal stress and tissue damage, yet the contribution of microglial ADP-sensitive receptors to AD progression remains poorly defined. Here, we investigate whether pharmacological blockade of microglial ADP receptor signalling modifies functional and molecular disease-related alterations in a progressive APP/Tau mouse model of AD-like pathology. To assess the role of microglial ADP receptor activity during disease progression, APP/Tau transgenic mice were chronically treated with an ADP receptor antagonist during early or advanced pathological stages. Cognitive and motor performance were evaluated using behavioural paradigms sensitive to disease-associated impairment, and biochemical and histological analyses were performed to evaluate treatment-induced changes in neuroimmune, neuronal and synaptic markers. Chronic blockade of ADP receptor signalling was associated with improved spatial memory performance in APP/Tau mice at both early and mild-advanced disease stages, with limited effects on motor-related outcomes. At the molecular and

histological levels, antagonist treatment selectively modulated AD-related neuroinflammatory and neurodegenerative markers in a stage-dependent manner. Early-stage treatment limited the emergence of disease-associated microglial phenotypes and astrocytic alterations, preserving less reactive glial profiles without broadly affecting homeostatic marker-positive populations. These changes were not evident following treatment at the mild-advanced stage, suggesting that the spatial memory improvement observed later in disease progression may involve distinct molecular mechanisms. Together, these findings identify microglial ADP receptor signalling as a stage-sensitive modulator of AD-related functional, neuroimmune and neurodegenerative alterations. The convergent behavioural, cellular and molecular effects observed following early intervention support targeting this pathway as a potential therapeutic strategy in AD. Importantly, the distinct response profiles observed across disease stages highlight the therapeutic window as a critical determinant of treatment outcome and underscore the need to consider not only pathological burden, but also disease context and progression, when developing microglia-directed interventions.

Disclosures: U. Fraga Bouzas: None. **Y. Jin:** None. **I. Pallás:** None. **Q. Sala Arcos:** None. **C.A. Saura:** None. **M. Puigdellivol Cañadell:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.13/U6

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

Title: Temporal dynamics of NF-κB-mediated transcriptional responses in glial cells: relevance to Alzheimer’s disease

Authors: *A. SARKAR[1], B. BHADURI[1], A. SINGH[1], C. SASAKI[1], D. SARANTOPOULOU[1], M. R. COOKSON[2], R. SEN[1];
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Abstract: Glial cells are central regulators of brain homeostasis, immune defense, and neurodegenerative disease progression. Among molecular pathways controlling glial function, nuclear factor kappa-light-chain-enhancer of B cells (NF-κB) is a central transcription factor regulating inflammation, stress responses, and cell survival. Despite extensive research, cell-type-specific activation patterns and transcriptional outputs of NF-κB in glial cells and their contributions to Alzheimer’s disease (AD) pathology remain poorly defined, limiting translation of molecular insights to therapies. We hypothesize that distinct glial populations (microglia and astrocytes) exhibit unique NF-κB activation patterns and transcriptional responses to inflammatory stimuli, that differentially but synergistically drive neuroinflammation and AD pathogenesis. To address this, our work focuses on defining basal and stimulus-induced subcellular dynamics of the NF-κB subunit RelA and identifying downstream NF-κB-targeted

gene networks across diverse model systems, including immortalized microglial and astrocytic cell lines, primary mouse glial cultures, and human induced pluripotent stem cells-derived microglia and astrocytes. As an initial phase, we examined NF-κB activation in immortalized microglia following bacterial lipopolysaccharide (LPS) exposure. Using Amnis imaging flow cytometry, we observed rapid RelA nuclear translocation peaking at 1-2 h and declining thereafter, indicative of transient NF-κB activation. qRT-PCR analyses revealed robust induction of early NF-κB responsive genes (*Nfkbia, Nfkbiz, Tnfaip3*, and *Tnfα*), followed by delayed upregulation of *Bcl2a1a* and *Gadd45b,* suggesting roles in cell survival and stress responses. Increased *Ccl3* expression highlights the chemotactic potential of activated microglia. Treatment with NF-κB inhibitor BAY 11-7082 attenuated LPS-mediated transcriptional responses, confirming NF-κB-dependent regulation of these genes. ChIP-qPCR analysis demonstrated enhanced RelA occupancy at regulatory regions of NF-κB target genes, including *Nfkbia* and *Tnfaip3*, within 1-2 h of LPS stimulation, supporting direct transcriptional regulation. Together, these findings demonstrate that LPS induces rapid but transient RelA nuclear translocation in microglia, coupled with temporally distinct inflammatory, chemotactic, stress-response, and pro-survival transcriptional programs. These results provide mechanistic insight into how microglial NF-κB activation contributes to neuroinflammatory processes relevant to AD pathogenesis.

Disclosures: A. Sarkar: None. **B. Bhaduri:** None. **A. Singh:** None. **C. Sasaki:** None. **D. Sarantopoulou:** None. **M.R. Cookson:** None. **R. Sen:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.14/U7

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

Title: Deciphering NF-κB-mediated neuroinflammatory pathways in Alzheimer’s disease using integrated in vivo and in vitro models

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Abstract: Neuroinflammation is a major contributor to the progression of Alzheimer’s disease (AD), involving complex interactions among neurons, microglia, and astrocytes that drive chronic inflammatory responses, synaptic dysfunction, and progressive neurodegeneration. However, NF-κB-mediated neuroinflammatory mechanisms in AD are still obscure. This study aims to investigate the spatio-temporal regulation of NF-κB-mediated neuroinflammation and its associated target genes in the 3xTg-AD mice and complementary *in vitro* systems. Distinct brain regions, including the hippocampus and cortex, from 3xTg-AD mice were analyzed at different stages of disease progression. Immunohistochemistry (IHC) was performed to evaluate microglial activation and astrocytic activity, which showed an increased expression of IBA-1 and

GFAP, respectively, in distinct disease stages. Simultaneously, upon assessing the neuronal integrity, amyloid-beta (Aβ) and phosphorylated tau (pTau) pathology revealed region-specific neurodegenerative alterations, which go in accordance with the progression of disease pathology. Gene expression analysis from hippocampus and cortex as well as Aβ exposed SH-SY5Y cells showed altered gene expressions of NF-κB-associated inflammatory target genes linked to neurodegeneration and chronic glial activation. Correlating neuronal dysfunction with region-specific inflammatory signatures and progressive glial activation in 3xTg-AD mice with selective NF-κB attenuation in different cell types will help to understand the temporal dynamics and spatial distribution of NF-κB signaling in both *in vivo* and *in vitro* AD models. This study holds significance in providing mechanistic insights into disease advancement and identifying potential molecular targets for therapeutic intervention in AD.

Disclosures: B. Bhaduri: None. **A. Sarkar:** None. **A. Singh:** None. **M. Kaila:** None. **R. Sen:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.15/U8

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

Support: 2T32NS007431-26

Title: Loss of Hippocampal Astrocyte Primary Cilia in Alzheimer's Disease Brains

Authors: *D. S. TART[1], S. S. KHAN[2];
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Abstract: Loss of Hippocampal Astrocyte Primary Cilia in Alzheimer’s Disease Brains
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DisclosuresD.S. Tart: None, **S. S. Khan:** None
Pathogenic hallmarks of Alzheimer’s disease (AD) include neuroinflammation and the accumulation of amyloid beta (Aβ) plaques, which coincide with neurodegeneration and cognitive dysfunction. In AD, astrocytes actively contribute to neuroinflammation by adopting a reactive phenotype. Astrocytes also play a crucial role in the clearance of Aβ plaques. Reactive astrocytes have been shown to possess elongated primary cilia – sensory organelles that protrude from the cell surface to survey the extracellular environment. Signaling at the primary cilium serves to regulate neuronal survival and attenuate the neuroinflammatory response of astrocytes. Recent studies have observed neuronal primary cilia loss in AD mouse models. However, it is poorly understood how alterations to primary cilia impact AD pathology and progression.

Moreover, the effect of AD pathology on astrocyte primary cilia is unclear, especially in human brain tissue. Immunohistochemistry (IHC) and super-resolution confocal microscopy on post-mortem human AD tissue sections revealed a significant loss of astrocyte primary cilia in the hippocampus (unpaired t-test). Analysis of 6-month-old 5xFAD and APP-SAA mice revealed a conserved loss of hippocampal astrocyte primary cilia. Interestingly, in 5xFAD mice, IHC and 3D surface reconstruction using Imaris revealed that plaque-associated astrocytes have significantly fewer primary cilia than non-plaque-associated astrocytes, and a significantly greater mean primary-cilia volume, as determined by a paired t-test. Our results reveal a novel pathology associated with AD hippocampal astrocytes in human and mouse tissue. Given the important role primary cilia play in promoting cellular homeostasis and survival, understanding the consequences of astrocyte primary cilia loss in AD may further our understanding of AD development and progression – potentially revealing new therapeutic targets.

Disclosures: D.S. Tart: None. **S.S. Khan:** None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.16/U9

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

Support: NIH grant RF1AG081362

Title: Astrocyte-specific inactivation of monoacylglycerol lipase delays Alzheimer's disease progression

Authors: *L. SUN, SUN;
The Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Alzheimer’s disease (AD) is the leading cause of dementia and remains without effective disease-modifying therapies. The endocannabinoid 2-arachidonoylglycerol (2-AG) plays a critical role in maintaining brain homeostasis but is rapidly degraded by monoacylglycerol lipase (MAGL). Previous studies have demonstrated that systemic inactivation of MAGL, either pharmacologically or genetically, reduces neuropathology and improves synaptic and cognitive function in AD models. However, systemic inactivation of MAGL produces adverse effects in both the central nervous system and the periphery. Our recent genetic studies in AD models show that deletion of MAGL in astrocytes, rather than in neurons, produces protective effects. The purpose of the present study was to determine whether intracerebroventricular (ICV) injection of AAV vectors specifically targeting astrocytic MAGL, a clinically relevant approach, can modify AD pathology and delay cognitive decline in APP transgenic (TG) mice when administered at a symptomatic stage, after Aβ pathology and cognitive deficits have already emerged. Our results show that astrocyte-specific silencing of MAGL significantly improved cognitive performance and restored synaptic integrity in APP-TG

mice. In addition, AAV-mediated MAGL knockdown markedly reduced Aβ deposition, attenuated neuroinflammation, and suppressed excessive synaptic pruning. Notably, astrocytic MAGL knockdown also reduced synaptic loss and mitigated cellular senescence associated with AD pathology. Collectively, these findings demonstrate that astrocyte-specific inhibition of MAGL can reverse multiple pathological and functional deficits even after disease symptoms have emerged. This study highlights astrocytic MAGL as a promising precision therapeutic target and suggests that AAV-based silencing of astrocytic MAGL could potentially be achieved through a single, minimally invasive intravenous injection as a disease-modifying therapeutic intervention for patients with AD.

Disclosures: L. Sun: None.

Poster

PSTR303: Alzheimer's Disease: Glial and Neuroinflammatory Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR303.17/U10

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

Support: Centre for Brain Research Intramural Grant

Title: Sex-specific astrocytic responses in the hippocampus and locus coeruleus shape memory outcomes during early Alzheimer's disease pathology

Authors: *R. ROY CHOUDHURY[1,2], S. KUSHWAHA[1,2], S. KARUNAKARAN[1];
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Abstract: Women are disproportionately affected by Alzheimer’s disease (AD), yet the mechanisms underlying sex-specific vulnerability and compensation remain poorly understood. One of the earliest brain regions affected is the locus coeruleus (LC), the brain’s primary source of norepinephrine (NE), which regulates arousal, circuit function, and neuromodulator-glia interactions through widespread projections. Astrocytes are key targets of NE signaling and play essential roles in synaptic maintenance, metabolic support, and memory-related plasticity. However, whether astrocyte-associated alterations within the LC and its downstream hippocampal circuit contribute to sex-specific differences during early amyloid pathology remains unclear. To address this, we examined male and female APPswe/PSEN1dE9 mice at 2-3 months of age, an amyloid-β oligomer-enriched pre-plaque stage, using astrocyte morphometric analyses, molecular profiling, biochemical assays, chemogenetic circuit manipulations, and contextual fear conditioning. Female APP/PS1 mice exhibited greater LC astrocyte-associated pathology than males, including disrupted dorsoventral astrocytic organization and increased complement-associated alterations at the astrocyte-dendrite interface. Despite these changes, female APP/PS1 mice retained 24-hour contextual fear recall, whereas male APP/PS1 mice displayed significant memory impairment. Chemogenetic activation of the LC-dorsal CA1

(dCA1) pathway increased hippocampal NE levels and partially restored contextual fear recall in male APP/PS1 mice, implicating disrupted LC-hippocampal signaling in early male vulnerability. Although female APP/PS1 mice initially preserved memory performance, delayed testing revealed impairments in memory persistence and contextual discrimination. Female APP/PS1 mice further exhibited increased astrocytic β2-adrenergic receptor expression in dCA1, elevated hippocampal lactate levels, and increased expression of monocarboxylate transporters (MCT1, MCT2, and MCT4) relative to male APP/PS1 and control mice. Pharmacological inhibition of monocarboxylate transporters with α-cyano-4-hydroxycinnamic acid impaired 24-hour contextual fear recall and abolished the apparent female advantage. Together, these findings reveal a sex-dependent dissociation between early LC pathology and cognitive outcome, whereby enhanced astrocytic β2-adrenergic receptor-lactate signaling within the hippocampus supports the preservation of memory function despite ongoing LC circuit alterations.

Disclosures: R. Roy Choudhury: None. **S. Kushwaha:** None. **S. Karunakaran:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.01/U11

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

Support: Privately Funded

Title: An oral metabolic therapeutic restores mitochondrial bioenergetics and modulates amyloid, oxidative, and inflammatory pathology in 5xFAD mice

Authors: *L. PEREZ DE SEVILLA;
Biocient, Torrance, CA

Abstract: Mitochondrial dysfunction, oxidative stress, neuroinflammation, and amyloid pathology are interconnected drivers of Alzheimer’s disease (AD), yet few therapeutic candidates demonstrate convergent activity across these disease domains. Here, we evaluated an oral metabolic therapeutic candidate in a 5xFAD mouse model using an integrated multimodal platform—high-resolution mitochondrial respirometry, Aβ multiplex immunoassay, plaque histology, proteomics with orthogonal Western blot validation, oxidative-stress assays, and longitudinal metabolic monitoring safety measures.The compound produced a robust bioenergetic signature across retina, cortex, and hippocampus, increasing mass-normalized mitochondrial respiration by approximately 25-46% (up to 46% at maximal uncoupled respiration), with the strongest effects at ETS capacity and Complex-I-independent respiratory states. Consistent with improved mitochondrial reserve capacity, ROS levels were restored to wild-type-comparable levels under treatment. Amyloid profiling by MSD immunoassay demonstrated significant modulation of Aβ biology, including reductions in Aβ42 and Aβ40 and a lowered Aβ42/Aβ40 ratio across complementary cohorts; these biochemical findings were

corroborated by Aβ plaque histology showing reduced plaque burden. Proteomic profiling revealed broad normalization of neuroinflammatory and disease-associated signaling pathways, including chemokine signaling, innate immune activation, and inflammatory remodeling. In parallel, the compound acted on cellular energy-sensing machinery as a bidirectional homeostatic modulator of AMPK, linking treatment exposure to both inflammatory pathway remodeling and metabolic regulation. Western blot analyses provided orthogonal confirmation of treatment-associated engagement of the mitochondrial and energy-signaling pathways identified by proteomics. Longitudinal weight and glucose measures revealed no compound-related adverse signal.Together, these multimodal data identify a differentiated metabolic therapeutic strategy with convergent effects on mitochondrial reserve capacity, oxidative stress, amyloid pathology, and neuroinflammatory signaling, supporting further translational development for AD and related neurodegenerative disorders.

Disclosures: L. Perez De Sevilla: A. Employment/Salary (full or part-time):; Biocient. 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 at Biocient. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biocient.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.02/U12

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

Support: CF-2023-G-971

Title: Neuroprotective and anti-inflammatory effect of scamonic acid as a potential candidate for the treatment of amyloidosis present in Alzheimer's disease.

Authors: *V. CAMPOS-PEÑA[1], C. RODRÍGUEZ-PÉREZ[2], D. TORAL[3];
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Abstract: Alzheimer´s disease (AD) is the leading cause of dementia and is characterized by progressive memory loss. It has been suggested that AD develops as a result of the amyloid-b peptide (Aβ) aggregation in the brain, which leads to neuronal toxicity and death. Therefore, Aβ could be a promising treatment target. The pharmaceutical interventions currently employed decelerate the progression of the disease; thus far, none have been capable of effecting a reversal. Consequently, there has been a recent surge of interest in the study of active components in specific herbal extracts, which may possess beneficial therapeutic properties for various diseases.

The present study aims to investigate the neuroprotective and anti-inflammatory effects of scamonic acid (SA) extracted from Ipomoea tyrianthina in an Aβ-induced neurotoxicity model. The objective of this study is to demonstrate the efficacy of SA administration in reducing inflammation and decelerating the neurodegenerative process. Preliminary results from our group appear to support this hypothesis. In addition, in silico assays have indicated that Aβ interacts with scamonic acid, which supports the hypothesis that it could be a potential therapeutic target. Finally, it is crucial to evaluate the molecular mechanisms involved in these processes to determine whether SA could potentially be used as a novel drug for treating amyloidosis in Alzheimer's disease and other amyloidopathies.

Disclosures: V. Campos-Peña: None. **C. Rodríguez-Pérez:** None. **D. Toral:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.03/U13

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

Support: Alzheimer's Association Grant AARF-21-848511
Spanish Ministry of Science Grant PID2022-138829OA-I00
Spanish Ministry of Science Grant CNS2023-144676
Spanish Ministry of Science Grant RYC2021-034046-I
Spanish Ministry of Science predoctoral fellowship PREP2022-000622

Title: Preventive senolytic treatment in the APP^{NL-G-F} knock-in model of Alzheimer’s disease modulates senescence and glial phenotypes in a sex-specific manner

Authors: *I. BENGOETXEA DE TENA, C. WÜST, L. WILKINSON, A. GUERRERO; Univ. of Barcelona (UB), Barcelona, Spain

Abstract: Alzheimer’s disease (AD) is the most prevalent neurodegenerative disorder, with aging as its primary risk factor. Cellular senescence, a stable and irreversible cell cycle arrest, contributes to both aging and early AD pathology. Senescent cells begin to accumulate in the brain prior to significant disease progression and secrete pro-inflammatory cytokines and proteases, potentially initiating or amplifying neuroinflammation and subsequent cognitive decline. Targeting cellular senescence at these early stages, before substantial neurodegeneration has occurred, may therefore represent a promising preventive strategy to delay or mitigate AD-related dementia and brain aging.
In this study, we investigated the effects of a chronic senolytic treatment in the APP^{NL-G-F} knock-in mouse model, which expresses humanized mutant amyloid precursor protein (APP) at physiological levels, avoiding overexpression artifacts and hence providing a translationally relevant paradigm for AD research. Treatment started at 1.5 months, prior to the onset of the pathology, and lasted until 3.5 months, covering the prodromal stages of disease progression.

Senescence, plaque pathology and gliosis-related markers were analyzed using immunohistochemistry and colorimetric imaging, as well as through ELISAs and targeted gene expression profiling by qPCR.
While plaque pathology was unaffected by the treatment, the levels of senescence-associated β-galactosidase (SA-β-Gal) activity, a key hallmark of senescence, were reduced in the cortex and hippocampus. Regarding Lamp1 immunofluorescence signal, a lysosomal protein which is a marker of dystrophic neurites, decreased hippocampal levels were observed with the treatment only in females, suggesting a differential, sex-specific response. The senolytic also reduced the proportion of disease-associated microglia (DAM, measured as $Iba1^{+}/Trem2^{+}$ signal), in this case specifically in males, and this was accompanied by an increasing tendency in homeostatic microglia ($P2Y12^{+}$ signal), indicating a potentially beneficial modulation of microglial states. Together, these findings underscore the importance of two still underexplored dimensions in neuroscience: the influence of sex and the central role of glial cells, particularly microglia, in modulating therapeutic responses in neurodegeneration. Our results also support the potential of senolytics in alleviating plaque-derived senescence and DAM, providing a basis for the future application of these compounds as a preventive therapy for AD.

Disclosures: I. Bengoetxea de Tena: None. **C. Wüst:** None. **L. Wilkinson:** None. **A. Guerrero:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.04/U14

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

Support: Alzheimer Society of Canada Proof of Concept Grant
CFI Leaders Opportunity Fund
Data Sciences Institute Doctoral Student Fellowship

Title: Neuroprotective peptide against amyloid-β oligomer toxicity rescues hippocampal sharp-wave ripple deficits and memory impairments

Authors: *Y. SUN[1], K. ZHANG[2], K. ANDO[5], T. SUZUKI[6], P. E. FRASER[3], K. TAKEHARA-NISHIUCHI[4];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Univ. of Toronto, TORONTO, ON, Canada; [3]Med. Biophysics, [4]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [5]Dept. of Biol. Sci., Tokyo Metropolitan Univ., Hachioji, Japan; [6]Dept. of Biol. Sci., Tokyo Metropolitan Univ., Chiba/ Chiba, Japan

Abstract: Alzheimer’s disease (AD) is characterized by progressive accumulation of amyloid-β (Aβ) and severe impairments in episodic memory. Consistent with these deficits, hippocampal sharp-wave ripples (SPW-Rs, 100-250 Hz), network oscillations critical for memory formation

and consolidation, are disrupted in several mouse models of AD. However, it remains unclear whether SPW-R abnormalities contribute directly to memory impairment or instead arise as parallel consequences of Aβ accumulation. To address this question, we treated the TgCRND8 mouse model of amyloidosis with the peptide therapeutic p3-Alcβ9-19 and recorded hippocampal CA1 activity during sleep before and after an object-location memory task. The p3-Alcβ9-19 is an 11-amino acid fragment derived from the neuron-specific membrane protein, Alcadein β/Calsyntenin-3. It corresponds to a sequence within endogenous p3-Alcβ37, which is markedly reduced in early-stage AD patients. Previous studies have shown that p3-Alcβ9-19 attenuates Aβ oligomer-induced calcium dysregulation and promotes neuronal survival (Hata et al., EMBO Mol Med, 2023). We found that subcutaneous administration of p3-Alcβ9-19 twice weekly for four weeks restored object-location memory in TgCRND8 mice to levels comparable to those of non-Tg controls. This behavioral improvement was accompanied by restoration of baseline SPW-R activity, which was significantly reduced in TgCRND8 mice. However, p3-Alcβ9-19 did not rescue the experience-dependent increase in SPW-R occurrence normally observed following the memory task. Elevated interictal epileptiform discharge rates were likewise unaffected by the treatment. Moreover, p3-Alcβ9-19 did not alter the burden of insoluble Aβ plaque depositions, suggesting memory was improved through neuroprotection rather than enhanced Aβ plaque clearance. We are currently extending these analyses to other hippocampal oscillations and CA1 neuronal spiking activity to further characterize the circuit mechanisms underlying the rescue. Together, these findings support a model in which Aβ oligomer toxicity contributes to memory impairment by disrupting hippocampal SPW-R activity and support p3-Alcβ9-19 as a promising neuroprotective strategy for restoring memory function in AD.

Disclosures: Y. Sun: None. **K. Zhang:** None. **K. Ando:** None. **T. Suzuki:** None. **P.E. Fraser:** None. **K. Takehara-Nishiuchi:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.05/U15

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

Title: Role of leptomerin in redox balance in the temporal lobe of rats with alzheimer´s disease induced by intrahippocampal injection of Aβ1-42 peptide

Authors: *T. SANCHEZ[1], I. CESAR ARTEAGA[3], A. D. DIAZ[2], D. JUÁREZ SERRANO[1]; [1]Ciencias Quimicas, [2]Inst. de Fisiologia, Benemerita Univ. Autonoma de Puebla, Puebla, Mexico; [3]Ciencias Quimicas, Benemerita Univ. Autonoma De Puebla, Puebla, Mexico

Abstract: Alzheimer’s disease (AD) is the most common form of dementia and is characterized by a complex, multifactorial and progressive pathophysiology. Among the most significant mechanisms driving its development are the accumulation of β-amyloid (Aβ) plaques and the

increase in oxidative stress, which consequently deteriorate neurotransmission mainly cholinergic, mediated by acetylcholine (ACh) in key brain regions such as the temporal lobe. Therefore, acetylcholinesterase inhibitors (AChEIs) have been proposed as important therapeutic strategies to preserve impaired cognitive and motor functions in AD. In this context, leptomerin has recently been suggested as a potential AChEI with neuroprotective properties. The objective of this study was to evaluate the effect of leptomerin on the redox balance in the temporal lobe of Wistar rats with an experimental model of AD induced by $A\beta_{1-42}$. Sixteen three-month-old male Wistar rats were used, randomly divided into four groups: Group 1: control without treatment. Group 2: Aβ group without treatment (with an intrahippocampal injection of $A\beta_{1-42}$). Group 3: Aβ group with treatment (which received 20 mg/ml leptomerin intraperitoneally). Group 4: treated with leptomerin without Aβ. After the treatment, the open field and novel object recognition tests (NORT) were applied. Subsequently, samples were collected from the temporal lobe to analyze oxidative stress markers (MDA, nitrites) and the activity of antioxidant enzymes (SOD, CAT). The results showed that leptomerin significantly improved short- and long-term memory in rats with AD, without altering motor function. It also reduced the levels of oxidative stress markers. On the other hand, the activity of antioxidant enzymes improved significantly in the treated groups. In conclusion, leptomerin showed relevant neuroprotective effects, improving cognitive function and the brain redox state.

Disclosures: T. Sanchez: None. **I. Cesar Arteaga:** None. **A.D. Diaz:** None. **D. Juárez Serrano:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.06/U16

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

Support: Central Research Institute, Novorex, Inc

Title: Development and therapeutic validation of a novel LRRK2 inhibitor NRX02067 in Alzheimer’s disease models

Authors: *J. LEE[1,2], E. KIM[3], H. PARK[4], W. SON[5], H. KO[6];
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Abstract: Leucine-rich repeat kinase 2 (LRRK2) regulates lysosomal function, mitochondrial homeostasis, and neuroinflammatory signaling and has emerged as a potential therapeutic target in Alzheimer’s disease (AD). We developed a brain-penetrant LRRK2 inhibitor, NRX02067, and evaluated its therapeutic potential in cellular and animal models of AD. A fragment-based

screening and in silico optimization strategy identified NRX02067 as a potent ATP non-competitive LRRK2 inhibitor. Among 25 candidate compounds screened using ADP-Glo assays, NRX02067 showed the strongest inhibition of LRRK2 activity, reducing kinase activity to 8.2% (WT) and 6.6% (G2019S) at 100 nM. Dose-response analysis demonstrated nanomolar potency, with IC_{50} values of 4.1 nM and 16.4 nM against WT and G2019S LRRK2, respectively.Functional validation showed that NRX02067 restored lysosomal dysfunction induced by hyperactive LRRK2, including recovery of lysosomal acidity and glucocerebrosidase activity. In comparison with reference LRRK2 inhibitors, NRX02067 exhibited superior efficacy in restoring lysosomal function.To evaluate neuroprotective effects in an AD-relevant context, primary cortical neurons were exposed to oligomeric amyloid-β (oAβ). oAβ significantly reduced cellular ATP production and metabolic activity, indicating impaired neuronal viability and bioenergetic dysfunction. NRX02067 treatment restored ATP levels and metabolic activity, as measured by CellTiter-Glo 2.0 and AlamarBlue assays. Furthermore, NRX02067 rescued synaptic PSD95 levels and improved mitochondrial morphology in oAβ-treated neurons.Therapeutic efficacy was further assessed in 5xFAD mice. Chronic oral administration of NRX02067 for five months significantly improved associative and spatial memory performance in fear conditioning and Morris water maze tests without major effects on locomotor or emotional-like behaviors.Together, these findings demonstrate that NRX02067 restores lysosomal function, protects neurons from Aβ-induced toxicity, and improves cognitive outcomes in an AD model. These results support LRRK2 as a promising therapeutic target in AD and highlight the potential of NRX02067 as a disease-modifying therapy for neurodegenerative disorders.

Disclosures: J. Lee: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research support from Novorex, Inc.. **E. Kim:** None. **H. Park:** None. **W. Son:** None. **H. Ko:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.07/U17

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

Support: Jane and Aatos Erkko Foundation

Title: Prolyl oligopeptidase ligand improves cognition via PP2A activation in 3XTG AD mouse

Authors: *H. CUI[1], **B. FASTRÉ**[1], X. ZHANG[1], T. T. MYÖHÄNEN[2];
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Abstract: motivation/problem statement Alzheimer’s disease pathology is marked by increasing amyloid plaque deposition and Tau hyperphosphorylation, and particularly Tau

accumulation drives the cognitive deficits. Current treatments are primarily symptomatic without disease-modifying efficacy. Our group has revealed that the prolyl oligopeptidase (PREP) ligands decrease tau phosphorylation-induced neurotoxicity and enhanced autophagy by activating protein phosphatase 2A (PP2A). We hypothesized that PREP ligand HUP-46 would attenuate AD pathology and preserve cognition in a transgenic AD mouse model. **methods/approach** In this study, we assessed cognitive performance in 6.5 month-old 3xTg-AD mice using Barnes maze after 28-day chronic administration of HUP-46 with intraperitoneal (i.p.) osmotic minipumps. We further used immunohistochemistry (IHC), western blotting (WB), and enzyme-linked immunosorbent assay (ELISA) to elucidate the mechanisms underlying the neuroprotective effect of HUP-46. **results** 4-week HUP-46 (10mg/kg/day) administration enhanced the Barnes maze performance compared with control animals. HUP-46 treatment in 3xTg-AD mice reduced soluble Tau5 and AT8, and insoluble Tau5 levels, indicating an overall attenuation of tau pathology. Furthermore, WB analysis shows a reduction in soluble Aβ , while the insoluble Aβ remains unchanged but ELISA showed decreased monomeric Aβ40/Aβ42 ratio. This suggests an effect on early amyloid species rather than deposited plaques. Additionally, HUP-46 increased LC3BII/LC3BI ratio, indicating modulation of autophagy-related processes. **conclusion/implications** Our results indicate that HUP-46 treatment effectively improves cognition (or memory?) in Barnes maze in 3XTG AD mouse after 4-week treatment. The therapeutic effects of HUP-46 are mainly driven by reducing tau-pathology and consistent with PP2A activation.

Disclosures: H. Cui: None. **B. Fastré:** None. **X. Zhang:** None. **T.T. Myöhänen:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.08/U18

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

Support: AEI Grant PID2022-138105OB-C22
La Marató de TV3 foundation grant 201433.30.31
Project PID2022-138105OB-C22, "Role of Human Reelin in the Mechanisms of Beta-Amyloid Propagation", funded by MCIN/AEI/10.13039/501100011033 and FEDER, EU.

Title: Reelin role in induced prion-like propagation of amyloids in mouse models

Authors: *K. HERRERA[1], D. ROSSI[2], M. PARDO[3,4], A. VILCHEZ-ACOSTA[4], A. PARCERISAS[4,1], F. SANT MASOLIVER[5,1], C. VERGARA LARROSS[5,1], M. VILA[6], A. TARUTANI[7,8], M. HASEGAWA[8], Y. MANSO[4,9], E. SORIANO[4,9], L. PUJADAS[1,4,9,10]; [1]Tissue Repair and Regeneration Lab. (TR2Lab), Inst. for Hlth. Res. and Innovation of Central Catalonia (IRIS-CC), Vic, Spain; [2]Vall d'Hebron Res. Inst. (VHIR), Barcelona, Catalonia, Spain; [3]Med. Oncology Service, Hosp. del Mar, Barcelona, Spain; [4]Univ. of Barcelona, Barcelona,

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Abstract: Amyloidogenic neurodegenerative proteinopathies are characterized by the accumulation of aberrantly folded protein aggregates, such as amyloid-β (Aβ) in Alzheimer's disease (AD) or α-synuclein (αS) in Parkinson's disease (PD). The spread of these proteinopathies across brain regions occurs through prion-like mechanisms involving transmissible protein species, a process in which the extracellular matrix (ECM) may play a modulatory role. Reelin, an ECM component, has been reported to interfere with the nucleation and aggregation of Aβ in both in vitro and in vivo models, suggesting a possible involvement in the regulation of protein aggregation and spreading. To explore whether Reelin may influence conformational transmissibility under physiological conditions, we used in vivo models of induced amyloidosis. Our results suggest that Reelin may influence the spreading of aggregating species within specific temporal windows. These findings support a potential role for Reelin as a modulator of prion-like propagation of amyloidogenic proteins and provide a framework to further investigate its contribution to mechanisms counteracting neurodegeneration.

Disclosures: K. Herrera: None. **D. Rossi:** None. **M. Pardo:** None. **A. Vilchez-Acosta:** None. **A. Parcerisas:** None. **F. Sant Masoliver:** None. **C. Vergara Larross:** None. **M. Vila:** None. **A. Tarutani:** None. **M. Hasegawa:** None. **Y. Manso:** None. **E. Soriano:** None. **L. Pujadas:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.09/U19

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

Title: In vitro Evaluation Platform for Anti-Ab Antibody Therapeutics

Authors: *L. WEN[1], X. DU[2];
[1]In vitro biology, Pharmaron, Beijing, China; [2]Pharmaron Beijing Co., Ltd., Beijing, China

Abstract: Amyloid β-peptide (Aβ) is a major neurotoxic driver of AD progression, and numerous research efforts have focused on suppressing the production, aggregation and deposition of endogenous Aβ. Anti-Aβ antibodies acts as valuable molecular probes for characterizing the structural features of Aβ aggregates, while also emerging as promising therapeutic candidates for AD treatment. Here we established a comprehensive *in vitro* evaluation platform encompassing molecular binding profiling, immune effector functional validation, neuroprotection assessment and blood-brain barrier (BBB) transcytosis analysis. $A\beta_{1-}$

$_{42}$ readily undergoes spontaneous self-assembly to form heterogeneous toxic aggregates. In this study, synthetic $A\beta_{1-42}$ peptides were incubated at 37°C for 24 hours to generate $A\beta_{1-42}$ protofibrils. Surface plasmon resonance (SPR) was performed to assess antibody binding to $A\beta_{1-42}$ monomers and protofibrils. The results revealed that all tested antibodies bound effectively to both Aβ monomers and protofibrils, and several candidates display preferential binding affinity toward toxic protofibril aggregates.Toxic Aβ oligomers and fibrils induce neuronal dysfunction and cell death, which are central to AD pathogenesis. We adopted a Thioflavin T (ThT) assay to evaluate the ability of antibodies to modulate Aβ aggregation. $A\beta_{1-42}$ monomers were co-incubated with candidate antibodies at 37°C for 6 hours and a marked, dose-dependent decrease in ThT fluorescence indicated potent suppression of Aβ aggregation. These results demonstrated that anti-Aβ antibodies confer prominent neuroprotective effects via inhibiting the formation and propagation of toxic Aβ aggregates.To characterize the antibody-mediated Aβ clearance activity, pHrodo Red-labeled $A\beta_{1-42}$ aggregates were prepared. J774.1 macrophages or human iPSC-derived microglia was co-cultured with the anti-Aβ antibody and pHrodo Red-labeled $A\beta_{1-42}$ aggregates, live-cell real-time imaging analysis demonstrated that the antibodies significantly enhanced microglial phagocytosis of Aβ aggregates. These findings confirmed strong antibody-dependent cellular phagocytosis (ADCP) activity, which enabled efficient clearance of pathological extracellular Aβ aggregates.In conclusion, we developed an integrated preclinical *in vitro* system for comprehensive assessment of anti-Aβ antibodies, including Aβ binding profiling, aggregation inhibition, neuroprotection, ADCP-based clearance and BBB transcytosis evaluation.

Disclosures: L. Wen: None. **X. Du:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.10/U20

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

Support: BrightFocus

Title: Investigating the Effects of Novel Probiotics on Alzheimer’s Disease Pathogenesis

Authors: *V. H. ANDERSON, L. C. BEAUCHAMP, L. A. PALUMBO, L. M. COX; Brigham and Women's Hospital, Harvard Med. Sch., Boston, MA

Abstract: The gut microbiome has been linked to neurodegenerative diseases, including Alzheimer’s disease (AD), in both humans and mouse models. There is potential for the use of probiotics to ameliorate AD, but they have not been specifically designed for AD treatment. Previous studies have shown that AD mice supplemented with short-chain fatty acids (SCFAs), including butyrate, had decreased Aβ deposition and tau hyperphosphorylation. Additionally, patients with AD have been found to have lower levels of butyrate-producing bacteria in their

microbiome compared to healthy controls. In this study, we chose three bacteria that are high butyrate producers. Through global metabolomic profiling, we found that these microbes also produce key metabolites that are reported to have neuroprotective effects. These bacteria were cultured and combined into a triple-probiotic cocktail for AD (TriAD). 5-month-old male APP/PS1 mice were orally gavaged with the TriAD probiotic twice per week for 8 weeks with weekly microbiome sampling. At 7 months of age, changes in AD pathology, peripheral immunity, and the microbiome were investigated. Notably, TriAD treatment decreased Aβ plaque number and increased pre- and post-synaptic co-localization in APP/PS1 mice. This was linked to a reduction in pro-inflammatory peripheral immune populations, including Tbet+ γδ and CD8 T cells in the spleen, TNFα, IFNγ, and Granzyme B+ γδ T cells in the mesenteric lymph nodes, and reduced Gal3+ CD4 and CD8 T cells in the spleen and mesenteric lymph nodes of APP/PS1 mice. From baseline to endpoint, probiotic treatment normalized the microbiota compositional differences between APP/PS1 and wild type mice, indicating possible amelioration of dysbiosis in the APP/PS1 mice. TriAD had a greater effect on the microbiome of the APP/PS1 mice than the wild type mice, indicating the TriAD probiotic may specifically target the dysbiosis occurring in AD. Taken together, these findings suggest that our TriAD probiotic ameliorates AD pathogenesis by lowering systemic inflammation and through the production of beneficial metabolites.

Disclosures: V.H. Anderson: None. **L.C. Beauchamp:** None. **L.A. Palumbo:** None. **L.M. Cox:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.11/U21

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

Support: Cure Alzheimer's Fund

Title: Targeting TMED receptors for therapeutic benefit in Alzheimer’s disease

Authors: *G. MONTI, C. A. DE MATA, J. PABLO, A. GREKA;
BROAD INSTITUTE OF MIT AND HARVARD - Cambridge, MA, Cambridge, MA

Abstract: Alzheimer’s disease (AD) is an incurable brain proteinopathy in which misfolded proteins progressively accumulate in neurons leading to cell death. The subcellular localization of aggregation-prone proteins in neurons is an important aspect of AD pathogenesis determined in part by the interacting partners of these toxic proteins. Rewiring the interactome of misfolded proteins to facilitate relocalization and degradation could therefore represent a new therapeutic approach to AD. TMED receptors have been previously implicated in toxic proteinopathies of the kidney and retina. In this study, we identified the AD-associated Amyloid Precursor Protein (APP) as a novel cargo for TMED receptors. By pharmacological intervention using a small

compound that specifically targets TMEDs, we observed retention of APP in the endoplasmic reticulum in neurons *in vitro* as well as *in vivo*, suggesting that TMED receptors are important for the ER-Golgi trafficking of APP. Importantly, treatment with the TMED-targeting compound significantly reduced amyloid plaque deposition in the brains of AD mice containing APP mutations (APP SAA). Beyond the canonical secretory pathway, we uncovered novel biological insights for TMED function at the ER-mitochondria interface, known to be enriched in APP and its derivatives. Through several biochemical and functional assays, we demonstrated that TMED depletion improved mitochondrial bioenergetics in human induced pluripotent stem cells carrying a mutation in APP linked to familial early onset AD, as well as restored metabolic balance in the APP SAA mouse model. Altogether, our work indicates that targeting TMEDs holds therapeutic potential for AD treatment through the restoration of organellar homeostasis.

Disclosures: G. Monti: None. **C.A. De Mata:** None. **J. Pablo:** None. **A. Greka:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.12/U22

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

Title: Structure-Activity Relationships of Small Molecules Targeting Intrinsically Disordered Monomeric Amyloid-β

Authors: *Y. QI;
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Intrinsically disordered proteins (IDPs) are challenging therapeutic targets due to their dynamic conformational ensembles and lack of defined binding pockets. Amyloid-β (Aβ), a central driver of Alzheimer's disease pathology, exemplifies this challenge. Although small molecules capable of modulating Aβ aggregation have been reported, the molecular determinants governing their recognition of monomeric Aβ remain poorly understood. This limits the ability to optimise initial hit compounds.To identify chemical features that promote small molecule-IDP interactions, we used 10074-G5 as a lead scaffold and synthesized a series of derivatives with systematic modifications to aromatic character, hydrophobicity, and hydrogen-bonding capacity. Binding interactions with monomeric Aβ were characterized using bio-layer interferometry (BLI), while effects on aggregation were evaluated using thioflavin-T (ThT) fluorescence assays.Across derivative classes, compounds designed to enhance aromatic interactions, hydrophobic contacts, or hydrogen-bonding potential generally exhibited stronger interactions with monomeric Aβ and improved anti-aggregation activity. Derivatives incorporating multiple favourable features showed the greatest improvements relative to the parent scaffold, suggesting that multiple non-covalent interactions cooperate in the recognition of disordered Aβ.These findings provide insight into the molecular basis of small molecule-IDP interactions and move

towards a structure-activity relationship framework for the rational design of aggregation inhibitors targeting Alzheimer's disease and related neurodegenerative disorders.

Disclosures: Y. Qi: None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.13/U23

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

Support: The STI2030-Major Projects Grant 2021ZD0200900

Title: Heightened Susceptibility of Spontaneous Type 2 Diabetic Macaque Brains to Synthetic $A\beta_{1-42}$ Oligomers Recapitulates the Alzheimer's Disease-like Phenotypic Spectrum

Authors: J. YAN, L. JU, C. ZHANG, Y. YANG, X. HUANG, ***F. YUE**;
Hainan Univ., Sanya, China

Abstract: Based on the amyloid cascade hypothesis, previous studies delivering $A\beta_{1-42}$ oligomers (AβO) into the brains of aged macaques have yielded only early-stage Alzheimer's disease (AD) pathological changes. Given that type 2 diabetes mellitus (T2DM) is a paramount modifiable risk factor for AD and has been shown to exacerbate AD pathology in macaques, we hypothesized that the T2DM brain environment could potentiate the pathogenic effects of AβO, thereby recapitulating late-stage AD-like pathology and cognitive decline. To test this hypothesis, AβO was delivered bilaterally into the dorsal hippocampal parenchyma of five spontaneously diabetic aged macaques and four healthy aged macaques. Following an average observation period of approximately 60 weeks, four out of five T2DM-AβO macaques exhibited a decrease in accuracy of greater than 15% on the 30-second Delayed Matching-to-Sample (DMTS) task, whereas only one out of four healthy AβO recipients showed a similar decline. Conversely, one T2DM-AβO macaque and three healthy AβO recipients showed a decline of less than 10%. Neuropathological evaluations revealed that, compared to healthy recipients, T2DM-AβO macaques developed a substantially greater burden of larger, more compact Aβ plaques across multiple brain regions. This was accompanied by a marked increase in phosphorylated tau pathology, most notably the emergence of hallmark ghost tangles in the hippocampus, as well as pronounced glial activation, exacerbated neuroinflammatory responses, and a widespread reduction in synaptic density. Crucially, while neurodegeneration and partial neuronal loss in healthy AβO recipients were restricted to the frontal cortex (FC), T2DM-AβO recipients suffered significant neurodegeneration and neuronal death across multiple brain regions. Furthermore, we defined an "AβO Susceptibility Index" as the rate of cognitive decline divided by the product of the cumulative AβO dose, the duration of intracerebral AβO induction, and the neuronal density in the FC. A higher index value indicates greater sensitivity to AβO induction; consistent with this, the susceptibility index was significantly higher in T2DM-AβO

macaques than in healthy recipients. Collectively, this study demonstrates that the brains of macaques with spontaneous T2DM exhibit heightened susceptibility to synthetic $A\beta_{1-42}$ oligomers. This synergistic interaction promotes pathological changes and cognitive decline that closely mirror those observed in late-stage AD patients, successfully recapitulating the clinical phenotypic spectrum of the disease.

Disclosures: J. Yan: None. **L. Ju:** None. **C. Zhang:** None. **Y. Yang:** None. **X. Huang:** None. **F. Yue:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.14/Web Only

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

Support: NIH Grant R01AG084699

Title: Effects of Intranasal VGF Derived TLQP-21 on Early- and Late-Stage Pathology in 5xFAD Model of Alzheimer's Disease

Authors: *M. BOSE[1,2], A. PAN[3], G. FARIAS QUIPILDOR[6], Y. HUANG[4], M. WANG[5], M. E. EHRLICH[7], S. R. J. SALTON[2];
[2]Neuroscience, Geriatrics and Palliative Med., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Neurosci., Icahn Sch. of Med. at Mount Sinai, Elmhurst, NY; [4]Neurol., Icahn Sch. of Med. at Mount Sinai, PARAMUS, NJ; [5]Genet. and Genomic Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Mount Sinai, New York, NY; [7]Neurology, Genet. and Genomic Sciences, and Pediatrics, Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: VGF (non-acronymic), a neurosecretory protein and peptide precursor implicated in Brain-Derived Neurotrophic Factor (BDNF) signaling, is selectively decreased by 10% per year in cerebrospinal fluid of mild cognitively impaired (MCI) subjects who progress to late-onset Alzheimer's disease (LOAD). Multi-omics studies of human postmortem LOAD brains identified VGF as a therapeutic target. In vivo, invasive administration of VGF and its processed neuropeptide TLQP-21 (named for N-terminal 4 amino acids and length) to the brain showed alleviated plaque/tangle load, attenuated neuroinflammation, induced neurogenesis, and promoted synaptic plasticity in 5xFAD mice. A non-invasive route of administration is required to advance TLQP-21 toward clinical development. We hypothesized TLQP-21 delivered intranasally could bypass the blood brain barrier to reach distal brain regions, specifically hippocampus, accumulating in therapeutically-significant amounts that recapitulate or surpass previous CNS delivery.
In Vivo Imaging System (IVIS) imaging confirmed Cy5-conjugated TLQP-21 is transported into the mouse brain and remains detectable for more than 48 hours. Ex vivo imaging confirmed and quantified hippocampal delivery, supporting administration of 60 μg/dose for chronic studies.

Unconjugated TLQP-21 or saline was then administered 3x/week for 6-weeks to early- (5 month) and late-stage (9 month) pathology male and female 5xFAD cohorts, During the last 2 weeks, behavioral assays [Barnes Maze (BM), Novel Object Recognition (NOR)] were conducted prior to euthanasia. Both wildtype and 5xFAD mice administered TLQP-21 showed improvements in BM memory and learning. Improved NOR recognition and object discrimination was observed in early- and late-stage female but not in male 5xFAD mice. Bulk transcriptomic analysis of prefrontal cortex revealed stage- and/or sex-dependent rescue signatures of pathology by TLQP-21. This was most robust in interferon-a and -g pathways in young female 5xFAD, with notable rescue in oxidative phosphorylation, reactive oxygen species, fatty acid metabolism, DNA repair, and MYC-target pathways in all female 5xFAD. Notable rescue signatures in male 5xFAD included angiogenesis, myogenesis, TGF-β signaling, hypoxia, and estrogen early response pathways. In early-stage male and female 5xFAD, the Aβ42/40 ratio was halved, plaque burden and size in hippocampus was decreased, and microglial activation was reduced in hippocampus and cortex. These changes were accompanied by hippocampal normalization of synaptic proteins PSD95 and synaptophysin, MAPK (ERK1/2) signaling, and pro/mature-BDNF ratios across cohorts.

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Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.15/U24

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

Title: Novelty as an inducer of cognitive resilience in a sporadic model of Alzheimer's Disease

Authors: *I. CARBAJAL AGUIRRE[1], E. HERNÁNDEZ-ORTIZ[2], F. BERMUDEZ-RATTONI[3];
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Abstract: Current therapies to cognitive improvement based on counteract beta-amyloid (Aβ) aggregation in sporadic Alzheimer's Disease (AD) have been poorly successful. Therefore developing therapeutic strategies to enhance the cognition and delay the progress are necessary. Cumulative evidence suggests Aβ1-42 oligomers are closely related to alterations in the catecholaminergic system, key for declarative memory, and the increased dopamine levels shift down memory impairment in AD-mouse models. Interestingly, novelty exposure environments (NExp) have been observed to increase basal dopamine levels in the hippocampus and in vitro studies suggest that Aβ1-42 oligomerization is blocked in presence of dopamine. However, the temporal impact of NExp on declarative memory improvement and a possible underlying neuronal mechanism remains unclear. In this study, the effect of NExp over different periods was

determined on the deposits of oligomeric Aβ1-42 forms in the hippocampus of induced murine models of sporadic-type AD in 3-month C57BL/6 subjects. A NExp protocol was developed involving the exposure of to repeated novelty objects in a time dependent-manner. Tyrosine hydroxylase (TH) positive fibers length was quantified using ImageJ software by analyzing skeletons. The analysis showed the NExp longest exposure time group presented the longest fibers; even the groups with shorter exposure had longer fibers than the control group, demonstrating a correlation with respect to NExp. Furthermore, an improvement in object location memory (OLM) was observed in the group exposed to the Nexp for 30 days and Aβ1-42, but not in the saline group, in contrast, 5 day for NExp was enough for improve the OLM in saline solution group but not for Aβ1-42. These results suggest that improvement in spatial recognition memory is dependent on both duration of the NExp and health vs disease condition, suggesting an underlying mechanism to mitigate damage caused by oligomers Aβ1-42 inducing resilience.

Disclosures: I. Carbajal Aguirre: None. **E. Hernández-Ortiz:** None. **F. Bermudez-Rattoni:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.16/U25

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

Support: Arizona Alzheimer’s Consortium
Van Winkle Fund
NIH NINDS R25 NS 076437
Burroughs Wellcome Fund PDEP

Title: Manual lymphatic drainage attenuates Alzheimer’s disease related biomarkers in the 5xFAD mouse

Authors: *M. J. BARTLETT[1,2], R. P. ERICKSON[2], F. POLK[3], J. FRYE[4], K. P. DOYLE[4], P. PIRES[5], M. WITTE[2];
[2]Surgery, [3]Physiological Sci. GIDP, [4]Immunobiology, [5]Physiol., [1]Univ. of Arizona Col. of Med., Tucson, AZ

Abstract: FDA approved immunotherapies slow cognitive decline for some individuals with Alzheimer’s disease (AD). However, they do not improve cognition, are costly, and can have significant side-effects. Therefore, new targets, approaches, and treatments for AD is an immediate necessity. Currently, there are no FDA approved therapies for AD that target the brain’s lymphatic system. Recent literature has demonstrated that the toxic protein, amyloid-beta (Aβ), which accumulates in the AD brain is cleared with interstitial and cerebrospinal fluid through a glymphatic—meningeal lymphatic vessel—deep/superficial cervical lymphatic vessel

pathway. Therefore, any impairment along this route can lead to inefficient drainage and pathological accumulation of Aβ, progressing to cognitive decline and eventually AD. We have previously shown that manual lymph drainage (MLD), a light skin massage technique used to reduce fluid accumulation in lymphedema, can reduce cognitive impairment in the 5xFAD mouse model. 5-month-old 5xFAD mice were treated with MLD for 15-minutes, twice per day, for two months. After completing behavioral testing, brain tissue was harvested to further investigate the impact of MLD on biomarkers of AD. First, we analyzed the effect of MLD on neurofilament light chain (NfL), a non-specific biomarker for neuronal injury. Both sham-treated and MLD-treated *5x-FAD* mice have significantly elevated plasma NfL compared to wild type (WT) mice. However, MLD significantly reduced plasma NfL compared to sham-treated *5x-FAD* mice suggesting a therapeutic effect (one-way ANOVA, with a Fisher's LSD *post hoc* test; $*p<0.05$; $n=5$ mice/group). We found a similar effect of MLD on the AD-specific biomarker, Aβ. The $A\beta_{42/40}$ ratio is significantly increased in the hippocampus of sham-treated and MLD-treated *5x-FAD* mice compared to WTs. Here, MLD also significantly reduced the hippocampal $A\beta_{42/40}$ ratio compared to sham-treated *5x-FAD* mice (one-way ANOVA, with a Fisher's LSD *post hoc* test; $*p<0.05$; $n=5$ mice/group). In conclusion, our pilot study provides proof-of-principle data for MLD's potential as a therapy for the treatment of AD.

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Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.17/U26

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

Title: Differential Induction of ARIA-like Pathologies by Anti-Aβ Immunotherapies in 5XFAD Mice: A Comprehensive Analysis of 12-Weeks Dosing with Clinical-Stage Antibodies

Authors: *L. ZHANG, J. TAN;
WuXi AppTec, Qidong, China

Abstract: Aims: Amyloid-related imaging abnormality (ARIA) has emerged as a principal safety concern not only for anti-amyloid-beta (Aβ) immunotherapies but also for microglia-mediated treatments for Alzheimer's disease. The pathophysiological mechanisms and the differential risk profiles remain incompletely understood. **Methods**: We treated 8-month-old 5XFAD mice (n=5-10 group) for 12 weeks with weekly (QW) intraperitoneal injections of: 1) Isotype-mIgG2 control, 2) 3D6-mIgG2 (murine precursor of bapineuzumab), 3) Aducanumab-mIgG2 (humanized), or 4) Remternetug-mIgG2 (humanized). ARIA-E was quantified via MRI T2-weighted hyperintensity once a week after treatment. Following perfusion, brain was collected and analyzed for Aβ clearance and microhemorrhages confirmation. **Results**: All active anti-Aβ groups showed significant reduction of parenchymal Aβ plaque load compared to

isotype control ($p<0.001$). However, they exhibited starkly different ARIA profiles. The 3D6-mIgG2 group demonstrated the highest incidence and severity of ARIA-E, and the aducanumab-mIgG2 group showed a moderate ARIA-E. Remarkably, the Remternetug-mIgG2 group, while achieving superior plaque clearance, displayed a significantly attenuated ARIA profile, with minimal microhemorrhages, comparable to the isotype control.**Conclusion**: This head-to-head study in a robust amyloidosis model demonstrates that the risk of inducing ARIA-like pathology is highly dependent on the specific antibody's properties. These preclinical findings provide critical mechanistic insights into ARIA pathogenesis and underscore the importance of antibody screening for mitigating treatment-emergent adverse events.

Disclosures: L. Zhang: None. **J. Tan:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.18/U27

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

Title: Human Adipose-Derived Mesenchymal Stem Cell Extracellular Vesicles Ameliorate Cognitive Impairment in Alzheimer's Disease Models

Authors: *A. R. R. DA CONCEICAO[1,2], J. MARINATTO[1], L. PINHEIRO[1], R. FRANCO[1], L. HEIMFARTH[1], F. G. BARROS-ARAGÃO[3], P. SOUZA[4], N. D. SILVA[5], F. G. DE FELICE[6]; [1]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Inst. of medical biochemistry, Rio de Janeiro, Brazil; [3]IDOR, Rio de Janeiro, ; [4]Federal Univ. of Santa Catarina, Curitibanos, Brazil; [5]Queen's Univ., Kingston, ON, ; [6]Ctr. for Neurosci. Studies, Queen's Univ. Ctr. For Neurosci. Studies, Kingston, ON, Canada

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide, imposing a substantial burden on patients, caregivers, and healthcare systems. Despite extensive research efforts, disease-modifying therapies remain limited, underscoring the need for innovative therapeutic strategies. Extracellular vesicles (EVs) derived from mesenchymal stem cells have emerged as a promising cell-free approach, as they can deliver bioactive cargo while minimizing risks associated with cell-based therapies, such as immune rejection and tumorigenicity. In this study, we investigated the neuroprotective potential of EVs derived from human adipose tissue mesenchymal stem cells in two preclinical mouse models of AD. One model was induced by intracerebral administration of amyloid-beta oligomers, while the second employed APP/PS1 transgenic mice. Male and female animals received intravenous injections of adMSC-derived EVs (EVsMSCs) or saline as a control. Cognitive performance was evaluated using memory-related behavioral assays, including the novel object recognition test and the Morris water maze. EVsMSC treatment significantly improved cognitive performance in both AD models compared to controls. Importantly, sex-dependent differences were observed, with male mice exhibiting a more pronounced

improvement in recognition and spatial memory following EVsMSC administration, whereas female mice showed a comparatively attenuated response. These findings indicate a greater susceptibility of males to the therapeutic effects of EVsMSC treatment across behavioral paradigms. Overall, our results demonstrate that EVs derived from human adMSCs mitigate cognitive deficits in preclinical models of AD while revealing sex-dependent differences in treatment responsiveness. This study supports EV-based therapies as a promising strategy for AD and reinforces the importance of incorporating sex-specific analyses in the development and optimization of novel therapeutic approaches.

Disclosures: A.R.R. Da Conceicao: None. **J. Marinatto:** None. **L. Pinheiro:** None. **R. Franco:** None. **L. Heimfarth:** None. **F.G. Barros-Aragão:** None. **P. Souza:** None. **N.D. Silva:** None. **F.G. De Felice:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.19/U28

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

Support: Intramural Research Program of the National Institutes of Health (NIH)

Title: Indy (Slc13a5) Deletion Attenuates Amyloid Pathology and Neuroinflammation and Promotes Mitochondrial Remodeling in the 5xFAD Mouse Model of Alzheimer’s Disease

Authors: *R. THAPA[1], R. A. MCDEVITT[1], P. ZUNDEL[1], K. KECKLER[1], N. PRICE[1], S. L. HELFAND[2], R. DE CABO[1];
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia, characterized by the deposition of amyloid plaques, tau tangles, neuroinflammation, metabolic dysfunction, and abnormal lipid droplet accumulation in glial cells. Recent evidence suggests that altered lipid metabolism and mitochondrial dysfunction contribute to the disease progression. Indy (Slc13a5) is a membrane citrate transporter that mediates the transport of citrate from the extracellular space into the cytoplasm, where citrate serves as the primary substrate for de novo lipogenesis and triglyceride synthesis. We hypothesize that knocking out Indy in mice (Indy KO) will limit the amount of citrate available for lipogenesis, thereby lowering lipid droplet accumulation in the brain and mitigating AD-related pathology. To investigate this, we crossed the 5xFAD amyloidogenic mouse model of AD with an Indy KO line and evaluated behavioral, histopathological, inflammatory, lipid metabolism, and mitochondrial outcomes at 4 and 8 months of age. Immunofluorescence analyses demonstrated that Indy KO reduced reactive astrogliosis as well as amyloid-β pathology in 5xFAD mice. Indy deletion also lowered the expression of inflammatory markers, including Iba1, Gfap, Il6, Il1b, and Ccl2, with more prominent effects observed in female mice. Indy KO seems to lower the expression of

genes/proteins involved in lipid metabolism and lipid droplet regulation, such as FASN, Lipin1, and HSL, in the brains of 5xFAD mice, suggesting reduced lipogenic signaling. Additionally, the KO of Indy results in upregulation of Ampkα, PGC-1α, VDAC, and TFAM, as well as components of Complexes II and IV of the electron transport chain, suggesting activation of energy-sensing pathways, mitochondrial biogenesis, and a potential shift toward improved mitochondrial bioenergetic capacity. Indy knockout in 5xFAD mice showed trends toward amelioration of spatial working memory deficits in cross-maze test and reduced hyperactivity in the open-field test. To summarize, our findings suggest that loss of Indy confers neuroprotection in the 5xFAD model by attenuating neuroinflammation, altering lipid metabolic pathways, and remodeling the mitochondrial oxidative phosphorylation machinery. Targeting citrate transport and lipid droplet metabolism may therefore be a promising therapeutic strategy to mitigate AD-associated pathology.

Disclosures: R. Thapa: None. **R.A. McDevitt:** None. **P. Zundel:** None. **K. Keckler:** None. **N. Price:** None. **S.L. Helfand:** None. **R. de Cabo:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.20/U29

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

Title: Behavioral and histopathological characterization of APP/PS1 mice expressing human APOE3 or APOE4

Authors: *R. RABL[1], S. R. STERLACE[4], **E. AUER**[2], A. FANTINA-WOBLISTIN[3], M. DAURER[1], M. PROKESCH[5];
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Abstract: The apolipoprotein E ε4 (APOE4) allele is the strongest genetic risk factor for late-onset Alzheimer’s disease (AD) and is associated with increased amyloid-β accumulation, cerebral amyloid angiopathy (CAA), and accelerated cognitive decline. Humanized APOE mouse models provide an opportunity to investigate the impact of APOE isoforms on disease progression and treatment-related outcomes. The present study aimed to characterize behavioral and histopathological phenotypes in APP/PS1 transgenic mice expressing human APOE4 (Arte10 × B6.129P2-Apoe^tm3(APOE*4)Mae N8) compared with APOE3-expressing mice (Arte10 × B6.129P2-Apoe^tm2(APOE*3)Mae N8) and C57BL/6 wild-type controls.
Male and female mice were evaluated at 8 and 11 months of age using a comprehensive behavioral test battery consisting of the Open Field Test, Y-Maze, Wire Hanging Test, Modified Irwin Test, Morris Water Maze, and Passive Avoidance Test to assess locomotor activity, anxiety-like behavior, motor function, neurological status, and cognitive performance. In a subgroup of animals, histopathological analyses were performed to assess amyloid-β plaque

burden, plaque morphology and distribution, and vascular amyloid deposition.
Behavioral analyses are ongoing and are expected to reveal genotype- and age-dependent differences in cognitive performance. Histopathological evaluation demonstrated distinct APOE isoform- and sex-dependent patterns of amyloid pathology. Expression of APOE3 was associated with reduced amyloid-β plaque burden and a more diffuse plaque distribution compared with Arte10 controls. In contrast, Arte10 × APOE4 mice exhibited overall plaque numbers comparable to Arte10 controls but showed increased vascular amyloid deposition, consistent with enhanced cerebral amyloid angiopathy. Across both APOE genotypes, female mice displayed more severe amyloid pathology than male mice.
Human APOE isoforms differentially modulate amyloid pathology in the Arte10 model, with APOE3 exerting a protective effect on parenchymal amyloid deposition and APOE4 promoting vascular amyloid accumulation. Together with the ongoing behavioral characterization, these findings highlight the importance of APOE genotype and sex as determinants of disease phenotype and therapeutic response. This model provides a valuable translational platform for evaluating APOE-dependent mechanisms underlying Alzheimer's disease progression and the safety of anti-amyloid therapies.

Disclosures: R. Rabl: A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **S.R. Sterlace:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **E. Auer:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **A. Fantina-Woblistin:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.21/U30

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

Support: NIH R01CA194409

Title: Breast Cancer Attenuates Amyloid Pathology Through Enhanced Peripheral Immune Cell Recruitment in a Compund Mouse Model of Alzheimer's Disease and Breast Cancer

Authors: *S. M. BROUXHON[1], M. O'BANION[2], S. KYRKANIDES[3];
[1]Neurosciences, [2]Neurosci., [3]Univ. of Rochester, Rochester, NY

Abstract: **Research Objective and Rationale:** Epidemiological and neuropathological studies have reported an inverse association between cancer and Alzheimer's Disease (AD), suggesting that tumor-derived systemic factors may influence neurodegenerative processes. However, the mechanisms underlying this relationship remain poorly understood.**Methods**: To investigate the impact of breast cancer on AD pathology, we utilized a transgenic mouse model combining

amyloid pathology (APP/PS1) with mammary tumor development (MMTV-Neu). Amyloid burden and immune cell populations were evaluated in ~15-month-old tumor-bearing and non-tumor bearing mice. Analyses were performed blinded to genotype and tumor status. Independent biological replicates and genotype-matched control groups were included throughout the study to ensure reproducibility and distinguish disease-specific from combinatorial effects.**Results:** Tumor-bearing AD mice exhibited an approximately 60% reduction in amyloid-β (Aβ) burden compared with age-matched AD controls. This reduction in Aβ burden was accompanied by increased infiltration of $CCR2^{+}$ monocytes, and enhanced accumulation of enlarged atypical multinucleated $CD45^{+}/CD68^{+}$ cells located near Aβ plaques and cerebral vasculature, consistent with an activated phagocytic phenotype. Notably, increased numbers of plaque-associated $CD45^{+}$ immune cells correlated with reduced Aβ plaque burden, supporting a role for peripheral immune-cell recruitment in amyloid clearance. These findings suggest that systemic pathways activated by breast cancer enhance endogenous mechanisms of Aβ removal.**Conclusions:** Reduced Aβ plaque burden in tumor-bearing APP/PS1:Neu+ mice is associated with increased accumulation of $CD45^{+}/CD68^{+}$ plaque-associated immune cells and enhanced CCR2+ monocyte recruitment. These data support a model in which tumor-induced systemic immune reprogramming enhances endogenous myeloid-mediated amyloid clearance. Identifying the circulating factors and immune pathways responsible for this effect, may uncover novel therapeutic targets that stimulate the brain's intrinsic capacity for amyloid removal and slow AD progression without requiring the presence of malignancy.

Disclosures: S.M. Brouxhon: None. **M. O'Banion:** None. **S. Kyrkanides:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.22/U31

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

Support: Centre for Brain Research Core Grant

Title: Sex differences and the role of estrogen in the synaptic underpinnings of Alzheimer's disease

Authors: *R. KOMMADDI, N. BASAVARAJU, A. GUPTA, R. HUSSAIN;
Ctr. for Brain Res., Bangalore, India

Abstract: Women have a higher incidence of Alzheimer's disease (AD) burden than men because they live longer than men. While women are protected until menopause, postmenopausal women have a much higher AD risk than men. However, the factors promoting the longer lifespan and rapid cognitive decline at post menopause in women in AD are not well understood. Estrogen is a neuroprotective agent, and postmenopausal age is associated with a decrease in estrogen levels. Numerous research studies have endeavored to elucidate the impact of sex

differences in the progression of AD pathology; nonetheless, the precise molecular pathways responsible for the onset and progression of the disease remain unclear. In this study, we aimed to investigate the clinical implications of sex differences in AD using mouse models. To understand how estrogen regulates recall memory and investigate the effect of estrogen on cognitive and synaptic functions in WT and AD female mice, we administered the estrogen intraperitoneally to the middle-aged mice (8-10 months). We found that recall memory deficits were restored in APP/PS1 female mice at 10 months. Next, we wanted to determine whether estrogen restores the F-actin levels and dendritic spine density, which was shown to be downregulated in APP/PS1 female mice. We found that the estrogen restored synaptosomal F-actin levels in APP/PS1 female mice. Further, estrogen treatment restored basal and apical dendritic length in the entorhinal cortex of 9-month-old APP/PS1 female mice. In this study, upon estrogen treatment, we also found that total spine density, mushroom spine, and thin spine density were significantly restored in 9-month-old APP/PS1 female mice compared to untreated APP/PS1 female mice. We conclude that our research will help to identify an estrogen-sensitive diagnostic biomarker based on a new molecular target for the early detection and monitoring of cognitive decline and develop novel therapeutics that mimic estrogen's neuroprotective effects without adverse side effects in Alzheimer's disease in women.

Disclosures: R. Kommaddi: None. **N. Basavaraju:** None. **A. Gupta:** None. **R. Hussain:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.23/U32

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

Title: Machine Learning Guided Sleep Staging in 5xFAD mice using Telemetry

Authors: *P. CHANANA[1], R. RABL[2], M. DAURER[2];
[1]Scantox Group, Graz, Austria; [2]Scantox Neuro GmbH, Grambach, Austria

Abstract: MACHINE LEARNING GUIDED SLEEP STAGING IN 5XFAD MICE USING IMPLANTED TELEMETRY Priyanka Chanana[1], Aaron Fantina-Woblistin[1], Laurenz Jauk[1], Martin Häring[1], Roland Rabl[1], Magdalena Daurer[1], Manuela Prokesch[1]*[1]Scantox Neuro GmbH, Neuropharmacology, Grambach, Austria*
Sleep disturbances are a common feature of Alzheimer's disease, yet their manifestation in preclinical models remains incompletely characterized. In this preliminary study, we performed sleep staging and activity tracking in 9-month-old female 5xFAD mice, a widely used transgenic model of amyloid pathology, and compared their behavioral states to wild-type (WT) controls. We employed lightweight implanted telemetry with two biopotential channels to record electroencephalography (EEG) and neck electromyography (EMG), along with activity and body temperature. Following implantation and recovery, animals were recorded continuously for one week. Using longitudinal monitoring and machine learning–guided state classification, we found

that 5xFAD mice exhibit a significant reduction in total sleep time accompanied by increased wakefulness. Bout analysis revealed further alterations in sleep architecture, with 5xFAD mice displaying fewer rapid eye movement (REM) sleep bouts that were of longer duration compared to WT animals. These findings indicate disruptions in both sleep quantity and structure in 5xFAD mice, reflecting key aspects of sleep dysregulation observed in Alzheimer's disease. Our results highlight the utility of combined sleep staging and activity tracking using implanted telemetry for detecting early and progressive changes in sleep behavior in neurodegenerative disease models.

Disclosures: P. Chanana: None. **R. Rabl:** None. **M. Daurer:** None.

Poster

PSTR304: Alzheimer's Disease: Therapeutic Strategies: Amyloidosis Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR304.24/V1

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

Title: AI-guided drug discovery using iPSC-neuron cellular models for Alzheimer's Disease

Authors: *Y. BIAN;
Univ. of Cambridge, CAMBRIDGE, United Kingdom

Abstract: Alzheimer's Disease (AD), being the most prevalent form of dementia, is characterised by pathological aggregation of peptide amyloid-beta (Aβ) in the brain. Aβ is an intrinsically disordered protein and therefore presents a challenging target for conventional structure-based drug discovery. Despite recent advances, there remains an urgent demand for effective therapeutics capable of modifying disease progression. Our group previously developed Ligand-Transformer, a machine-learning pipeline for identifying small molecules that bind to protein targets, and applied it to Aβ. Candidate binders were initially validated using *in vitro* aggregation kinetic assay. The top two compounds, named D4 and D8, were able to delay Abeta aggregation half-times by 6.3 times and 3 times. They were further validated by Biolayer interferometry to bind Abeta monomers with Kd values of 4.59 ± 0.17 μM and 6.62 ± 1.33 μM, respectively. Here, we evaluated their potency in a human neuron cellular model. Induced pluripotent stem cells (iPSCs) were differentiated into neurons and treated on day 25 and 27 with freshly purified Aβ monomers and preformed Aβ seeds to establish a robust seeded aggregation driven by secondary nucleation. D4 or D8 was administered simultaneously at 250 and 500 nM. Cultures were maintained until day 30, when the amount of Aβ aggregate formation were quantified by immunocytochemistry. Both molecules exhibited excellent potency by reducing the number of Aβ puncta by over 50% relative to DMSO controls. Meanwhile, the total area of puncta was also reduced by more than 50%. No overt signs of neuronal toxicity were observed under the conditions tested. These findings support D4 and D8 as promising lead compounds for further optimisation. Moreover, this work demonstrates our machine-learning-guided ligand

discovery as a strategy for developing new therapeutics for treating neurodegenerative diseases associated with protein misfolding.

Disclosures: Y. Bian: None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.01/V2

Topic: C.03. Parkinson’s Disease

Support: ASAP020572

Title: Defining the Role of Locus Coeruleus-Prefrontal Cortex Interactions in Parkinson’s Disease Cognitive Impairment

Authors: *H. HOSSEINI[1], S. VICINI[2], H.-Y. CHU[3];
[1]Univ. of Georgetown, Washington, DC; [2]Dept Parmacology & Physiol., Georgetown Univ. Med. Ctr., Washington, DC; [3]Georgetown Univ., Washington DC, DC

Abstract: Cognitive impairments are common and debilitating non-motor symptoms of Parkinson's disease (PD) that are closely linked to early degeneration of the locus coeruleus-norepinephrine (LC-NE) system. Despite the importance of norepinephrine in regulating attention, executive function, and cortical state, the cell-type-specific mechanisms by which LC signaling modulates prefrontal circuits remain poorly understood. We hypothesize that noradrenergic signaling from the LC maintains cognitive function through cell-type-specific modulation of prefrontal circuits and that disruption of this signaling contributes to the network dysfunction underlying cognitive decline in PD. This project investigates how LC noradrenergic input differentially influences excitatory and inhibitory neuronal populations within the medial prefrontal cortex (mPFC) and shapes network activity. Using optogenetics, genetically encoded NE sensors, and calcium imaging, we characterized neuronal and network responses to LC activation. The ongoing work focuses on understanding the behavioral implications of cell-type-specific modulation of mPFC circuits by the LC-NE system in health and parkinsonian states.

Disclosures: H. Hosseini: None. **S. Vicini:** None. **H. Chu:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.02/V3

Topic: C.03. Parkinson's Disease

Title: Validation of a primary mesencephalic culture model reveals differential responses of oligodendrocyte lineage cells to α-synuclein pathology in Multiple System Atrophy

Authors: *E. BEZARD[1], K. HARHOURI[3], J. SANTIAGO MICHEA[4], M. OUAMER[3], J. CONFAIS[5], M. XILOURI[6], C. MAZZOCCO[7], P.-O. FERNAGUT[1], B. DEHAY[2], R. STEINSCHNEIDER[8];
[1]Inst. of Neurodegenerative Dis., Univ. of Bordeaux, Bordeaux, France; [2]Inst. of Neurodegenerative Dis., Univ. of Bordeaux, Bordeaux Cedex, France; [3]Neuronexperts SAS, Marseille, France; [4]Neuronexperts SAS, MARSEILLE, France; [5]Cynbiose, Saint-Consorce, France; [6]Biomed. Res. Fndn. of the Acad. of Athens, Athens, Greece; [7]Inst. of Neurodegenerative Dis., Univ. fo Bordeaux, Bordeaux, France; [8]NeuronExperts, Marseille, France

Abstract: Multiple System Atrophy (MSA) is a rapidly progressive and fatal synucleinopathy known as an atypical Parkinsonian disorder. MSA is characterized by oligodendroglial inclusions composed of α-synuclein (α-syn) aggregates, leading to neurodegeneration. The mechanisms underlying oligodendroglial vulnerability remain poorly understood.We established an in vitro model of MSA and investigated the differential susceptibility of oligodendrocyte lineage cells to pathological α-synuclein accumulation.Primary mesencephalic cultures from embryonic C57BL/6 mice (E14) were cultured for 7 days and exposed to synuclein preformed fibrils (PFFs) for an additional 7 days to induce seeding and propagation of pathological α-synuclein at different maturation stages. Accumulation of phosphorylated α-synuclein (pS129-α-syn) was assessed in PDGFRα-positive oligodendrocyte progenitor cells (OPCs) and MAG-positive mature oligodendrocytes (MOs). Cell survival and neurite length were quantified following PFF treatment.Synuclein PFF exposure during 7 days induced robust accumulation of pS129-α-syn in both OPCs and MOs. Despite harboring pathological α-syn, OPCs survival was not significantly altered. In contrast, MOs displayed reduced survival together with a marked shortening of their neurite's length, indicating a selective vulnerability of differentiated oligodendrocytes to α-syn pathology.We established a primary mesencephalic culture model reproducing key aspects of MSA-related α-syn pathology. Our findings demonstrate that MOs are associated with increased susceptibility to α-syn-induced toxicity. While OPCs tolerate pathological α-syn accumulation without loss of viability. The selective vulnerability of mature oligodendrocytes may result from the progressive accumulation of pathological α-synuclein during oligodendroglial maturation and/or from the higher metabolic demands associated with myelin maintenance. Conversely, the preservation of OPCs may reflect enhanced stress-response mechanisms and compensatory progenitor renewal. These results provide new insight into oligodendroglial degeneration in MSA and identify mature oligodendrocytes as a key cellular target of α-syn toxicity.

Disclosures: E. Bezard: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac Holding. **K. Harhouri:** A. Employment/Salary (full or part-time):; Neuronexperts SAS. **J. Santiago michea:** A. Employment/Salary (full or part-time):; Neuronexperts SAS. **M. Ouamer:** A. Employment/Salary (full or part-time):; Neuronexperts SAS. **J. Confais:** A. Employment/Salary (full or part-time):; Cynbiose. **M. Xilouri:** None. **C. mazzocco:** None. **P. Fernagut:** None. **B. Dehay:** None. **R. Steinschneider:** E. Ownership Interest (stock, stock options, royalty, receipt of

intellectual property rights/patent holder, excluding diversified mutual funds); Neuronexperts SAS.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.03/V4

Topic: C.03. Parkinson’s Disease

Support: NIDA Intramural Research Program

Title: Investigating Golgi apparatus morphology in rat midbrain neurons

Authors: *A. HARR, M. HAYDOCK, L. GREER, B. K. HARVEY;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Parkinson’s disease (PD) is a neurodegenerative movement disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). A hallmark pathological feature of PD is the formation of insoluble inclusions called Lewy bodies, which are comprised of misfolded alpha-synuclein as well as other proteins. Although this Lewy body pathology is seen throughout various brain regions, degeneration is mainly confined to nigral dopamine neurons in PD patients, suggesting that these neurons have a unique susceptibility to degeneration. Studies of post-mortem tissue from PD patients, as well as animal and cellular models of PD, have observed fragmentation of the Golgi apparatus in dopaminergic neurons, including those lacking Lewy bodies, suggesting that Golgi apparatus dysfunction is a feature of PD and occurs early in disease progression. The Golgi apparatus is a key hub for protein folding and trafficking, and disruptions to these processes are associated with aggregation of misfolded proteins and cell death across many degenerative diseases. Thus, understanding Golgi apparatus function in dopaminergic neurons could yield insights into Parkinson’s disease progression. Here we characterize Golgi apparatus morphology in neuronal subtypes in the rat midbrain. We used immunofluorescence to label midbrain tissue for tyrosine hydroxylase (TH), neuronal nuclei (NeuN), and GM130, a cis-Golgi matrix protein and imaged the SNc and ventral tegmental area (VTA) using confocal microscopy. An image analysis software was used to create 3D reconstructions of the of the immunolabeling and quantify Golgi volume in neurons in these regions. We found that TH+ SNc neurons have larger Golgi compared to TH- SNc neurons and all neurons in the VTA, suggesting that nigral dopaminergic neurons have a unique protein trafficking system compared to other midbrain neurons. These results provide insight into subcellular structures controlling proteostasis in dopaminergic neurons and may provide clues to the mechanisms of selective degeneration of nigral dopamine neurons in Parkinson’s disease.

Disclosures: A. Harr: None. **M. Haydock:** None. **L. Greer:** None. **B.K. Harvey:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.04/V5

Topic: C.03. Parkinson's Disease

Support: UNSW Medicine Neuroscience, Mental Health and Addiction Theme and SPHERE grant
Australian Government Research Training Program (RTP) Scholarship

Title: Effects of tyramine-derived trace amines and tryptamines on SH-SY5Y cell viability in a rotenone-induced model of Parkinson's disease

Authors: *K. CARRUTHERS[1], A. K. WALKER[2], T. M. FURLONG[1];
[1]The Univ. of New South Wales, Sydney, Australia; [2]Neurosci. Res. Australia, Randwick, Australia

Abstract: Tyramine-derived trace amines (tyramines) and tryptamines are naturally occurring compounds present in dietary sources and plant species such as *Phalaris* grass. It has been proposed that consumption of these compounds may contribute to neurological syndromes resembling Parkinson's disease (PD) in *Phalaris* grazing livestock such as sheep and kangaroos; however, the cytotoxic effects of these compounds have not been systematically characterised *in vitro*. The current study investigated the cytotoxic and modulatory effects of three tyramines (tyramine, N-methyltyramine, and hordenine) and three tryptamines (tryptamine, 5-methyltryptamine, and 5-methoxytryptamine) across a broad concentration range (10 nM - 10 mM) in undifferentiated human neuroblastoma SH-SY5Y cells using an *in vitro* rotenone toxin (30 nM) model of PD. Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay across ≥ 4 independent experiments, with data normalised to vehicle controls. Each compound was tested alone and in combination by chemical class (tyramine or tryptamine) to model compound co-occurrence in *Phalaris* grass. Cells were also pre-treated with the compounds (24 hours) prior to rotenone exposure (an additional 24 hours) to evaluate modulation of rotenone-induced cytotoxicity. When tested independently, tyramines only reduced cell viability at supraphysiological concentrations (≥ 1 mM), whereas tryptamines reduced viability at lower concentrations (≥ 100 µM), indicating concentration and structure-dependent cytotoxicity. Combined treatment of the tyramines did not affect cell viability at 10 µM or 100 µM, suggesting no additive effects. In contrast, combined tryptamine treatment produced cell viability decreases at 10 µM when all three compounds were present, and at 100 µM when 5-methyltryptamine was combined with other tryptamines, supporting structure-dependent cytotoxicity. Compound pre-treatment did not modulate rotenone-induced cytotoxicity at low concentrations; however, viability reductions at high concentrations may reflect compound-toxin interactions. Overall, these findings demonstrate that tryptamines, particularly 5-methyltryptamine, are more cytotoxic than tyramines. However, these effects were largely restricted to supraphysiological concentrations, indicating limited cytotoxic effects and limited modulation of rotenone-induced cytotoxicity at physiologically relevant concentrations.

Therefore, the current study does not provide evidence of these compounds contributing to the PD-like neurodegeneration observed in *Phalaris* grazing livestock.

Disclosures: K. Carruthers: None. **A.K. Walker:** None. **T.M. Furlong:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.05/V6

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson's Research

Title: Mechanistic characterization of novel potential Parkinsonian toxicants Identified through qHigh-Throughput Screening of MT1G expression

Authors: *M. GARCIA AGUILAR, Z.-B. TONG, R. HUANG, S. SAKAMURU, M. XIA, D. GERHOLD;
Natl. Ctr. for Advancing Translational Sci., NIH, Rockville, MD

Abstract: The etiology of Parkinson's disease (PD) remains incompletely understood, although environmental chemical exposures are increasingly recognized as important contributors to disease susceptibility. To identify previously unrecognized environmental factors linked to PD, RNA sequencing was performed in differentiated LUHMES (dLUHMES) neurons exposed to seven established Parkinsonian neurotoxicants. Comparative transcriptomic analysis revealed shared gene expression changes across treatments, with *MT1G* emerging as the most consistently and robustly induced gene. *MT1G* encodes Metallothionein-1, a metal-binding protein involved in metal homeostasis and protection against oxidative stress, both strongly implicated in PD pathogenesis. Using CRISPR/Cas9, LUHMES cells were engineered to express luciferase under endogenous *MT1G* regulatory control, enabling development of a quantitative high-throughput screening reporter assay in 1536-well format. Screening of the LOPAC and Tox21 10K libraries identified 18 compounds that induced *MT1G* expression and were selected for mechanistic characterization. Since mitochondrial dysfunction is a hallmark of PD, compound effects were evaluated in dLUHMES cells cultured in galactose-containing medium, which increases sensitivity to mitochondrial toxicants. Classical mitotoxicants such as rotenone displayed markedly enhanced potency under these conditions, whereas *MT1G*-inducing compounds showed no significant change in toxicity, suggesting mitochondrial dysfunction is not their primary mechanism. Consistently, TMRE-based measurements revealed no evidence of early mitochondrial depolarization following exposure. Given the role of metal imbalance in PD and the strong induction of *MT1G*, the involvement of transition metals was further investigated. Compounds were hypothesized to act as ionophores or metal chelators. Co-treatment with metal chelators rescued cell viability for several compounds, indicating that metal availability modulates their toxicity. Direct metal-chelating activity was further assessed using ferrozine-

based iron assays and copper quantification assays, which demonstrated that several compounds possess also metal-chelating properties. potentially disrupting the availability of metals required for essential enzymatic processes and cellular survival. Together, these findings suggest several chemotype candidates from screening of chemical libraries that may contribute to neurotoxicity in Parkinson's disease. Mechanistic characterization suggests that neurons may be vulnerable to disruption of metal distribution and to oxidative stressors.

Disclosures: M. Garcia Aguilar: None. **Z. Tong:** None. **R. Huang:** None. **S. Sakamuru:** None. **M. Xia:** None. **D. Gerhold:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.06/V7

Topic: C.03. Parkinson's Disease

Support: NIDA Intramural Research Program

Title: Increasing KDEL receptor expression in the rat midbrain causes ER stress and a loss of dopaminergic neuron phenotype

Authors: *L. K. GREER[1], A. HARR[2], R. SVARCBAHS[3], K. E. SAVELL[4], A. E. TISCHER[3], A. F. HOFFMAN[5], M. MICHAELIDES[6], B. T. HOPE[7], C. R. LUPICA[8], B. K. HARVEY[9]; [1]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [2]Natl. Inst. on Drug Abuse, Medford, NJ; [3]Natl. Inst. on Drug Abuse, Baltimore, MD; [5]Cell. and Neurocomputational Systems Branch/Electrophysiology Res. Section, [4]NIH, NIDA IRP, Baltimore, MD; [6]NIDA/NIH, Baltimore, MD; [7]Behav Neurosci, NIH/NIDA, Baltimore, MD; [8]Cell. Neurobio., NIH/NIDA-IRP, Baltimore, MD; [9]MMCSI, NIDA - NIH, Baltimore, MD

Abstract: Dopaminergic neurons (DANs) are key regulators of reward and movement and are uniquely sensitive to degeneration in Parkinson's disease (PD), the second most common neurodegenerative disease. A common feature found in many PD animal models and human post-mortem PD tissue is the prevalence of cellular stress and protein misfolding, representing disruptions in proteostasis. The endoplasmic reticulum (ER) and Golgi apparatus are primary sites of protein folding and protein processing, which are mediated by ER resident proteins that process newly translated proteins in the ER lumen and chaperone them to the Golgi. KDEL receptors (KDELRs) are Golgi-localized transmembrane proteins that help maintain ER protein residency by mediating retrograde transport from the Golgi back to the ER, particularly during cellular stress. We previously showed that KDELR gene expression and retention of ER proteins is increased to maintain protein homeostasis during cellular stress. Given that ER resident proteins are central to protein processing, changes to KDELR expression could impact protein homeostasis through controlling the localization of ER resident proteins and contribute to pathologies where ER stress is implicated. The role of KDEL receptors in the brain are

understudied, and their function in DANs and resulting dopamine dynamics is unknown. In the current study, we increased expression of KDELR in the rat midbrain and examined effects on dopaminergic neurons at the transcriptional and functional levels. Through single nucleus RNA-sequencing, we found that increased KDELR expression in DANs results in decreased transcription of genes related to dopaminergic and synaptic function in DANs and mature oligodendrocytes. Additionally, we characterized the functional consequences by fast scan cyclic voltammetry and autoradiography and observed a decrease in dopamine release and dopamine transporter binding, respectively. Finally, we demonstrate that increasing KDELR expression causes Golgi fragmentation in DANs, resulting in the disruption of secretory organelle machinery. These results suggest that modulating KDEL receptors alters cellular machinery and antagonizes the dopaminergic neuronal phenotype, resulting in decreased expression of dopaminergic and neuronal genes in DANs and oligodendrocytes, as well as decreased dopaminergic function. This study provides new insight into mechanisms of neuronal proteostasis and its relationship with maintaining the dopaminergic neuron phenotype.

Disclosures: L.K. Greer: None. **A. Harr:** None. **R. Svarcbahs:** None. **K.E. Savell:** None. **A.E. Tischer:** None. **A.F. Hoffman:** None. **M. Michaelides:** None. **B.T. Hope:** None. **C.R. Lupica:** None. **B.K. Harvey:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.07/V8

Topic: C.03. Parkinson’s Disease

Title: Combining functional cellular assays and multiparametric high-content imaging to characterise lysosomal function in neurodegenerative disease drug discovery.

Authors: *M. HELLEY, B. TUCK, I. POTAPOV, L. BEVAN, L. GLENNON, A. HOWARD, F. TUVERI, D. TAMS, H. WEIR, C. F. BENTO, M. AHN;
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Abstract: Lysosomal dysfunction is a central mechanism of neurodegenerative pathology, linking rare lysosomal storage disorders to more common conditions like Parkinson’s and Alzheimer’s diseases. Translating these pathological observations into therapeutics requires a granular understanding of how lysosomal machineries fail. Here, we describe a dual approach to studying lysosomal function in various cellular systems. Firstly, we have developed a multi-assay platform designed to dissect the multifaceted roles of lysosomes. This includes intra-lysosomal pH quantification, lysosomal ion conductance, and in situ monitoring of lysosomal biogenesis and hydrolase activity. Furthermore, we monitor downstream organelle stress responses via TFE3 nuclear translocation and correlate changes to lysosomal function with neuronal and microglial health readouts. Notably, our high-content imaging approach reveals significant spatial heterogeneity in lysosomal enzyme activity and function across disease-

relevant cell types. Secondly, we have developed an unbiased informatics pipeline coupled with multiparametric high-content imaging. By utilising over 430 morphometric and intensity-based features from lysosome-stained populations, we have successfully mapped distinct lysosomal disease signatures. For example, chemical inhibition of lysosomal cholesterol transport yields a clearly defined lysosomal storage disorder signature, providing a sensitive baseline for therapeutic rescue. By combining functional assays and deep phenotypic readouts with our proprietary structure-based drug discovery platform, we aim to generate the next generation of therapeutics to restore lysosomal function in disease.

Disclosures: M. Helley: A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **B. Tuck:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **I. Potapov:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **L. Bevan:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **L. Glennon:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **A. Howard:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **F. Tuveri:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **D. Tams:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **H. Weir:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **C.F. Bento:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals. **M. Ahn:** A. Employment/Salary (full or part-time):; Astex Pharmaceuticals.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.08/V9

Topic: C.03. Parkinson’s Disease

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NIH Grant NS108675
NIH T32 5T32GM135028
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NIH F31 1F31NS135928-01A1

Title: Coronin1C modulates lysosomal activity and Alpha-Synuclein pathology by negatively regulating Rab27b

Authors: *K. SCHOLZ[1], C. CRAIG[2], L. MATHENY[2], T. A. YACOUBIAN[2];
[1]Univ. of Alabama, Birmingham, Hoover, AL; [2]Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Rab27b is a small GTPase that our lab has implicated in Alpha-Synuclein (aSyn) disorders including Parkinson’s Disease (PD) and Dementia with Lewy Bodies (DLB). We have previously shown that Rab27b facilitates lysosomal activity and can protect against aSyn

pathology in *in vitro* models. It is also elevated in human brain tissue from subjects with PD and DLB relative to age-matched controls, functioning as a potential therapeutic target in Synucleinopathies. We have recently begun exploring the Rab27b-interacting protein Coronin1c (Coro1c). We found that knockdown (KD) of Coro1c in an inducible aSyn overexpression cell model resulted in elevated lysosomal degradative function, as measured by the proteolytic unquenching of both the generalized substrate DQBSA and of specific substrates for the lysosomal enzymes Cathepsin D and Glucocerebrosidase. Gross lysosomal counts were not altered, indicating that the observed effects may be localized to the enzymes themselves. We also assessed aSyn solubility using serial fractionation with Triton-X-100 followed by SDS, and we found that Coro1c KD protects against the accumulation of both soluble and insoluble aSyn. Collectively, Coro1c KD mimics phenotypes we have previously observed with Rab27b overexpression (OE), and we thus hypothesized that Coro1c binds to and inactivates Rab27b, reducing its lysosomal activity. We validated previously published work showing that Coro1c selectively interacts with the GDP-bound, inactive form of Rab27b, and found that Coro1c KD results in elevated Rab27b membrane association, which is a common proxy for GTPase activity. We then generated double-knockdown cell culture models and found that Coro1c KD does not elevate DQBSA signal if Rab27b is also knocked down, indicating that Rab27b expression is necessary for Coro1c to alter lysosomal function. We have previously shown that Rab27b OE boosts lysosomal degradative activity, and here we find that the double OE of Coro1c alongside Rab27b abolishes this effect. Like Rab27b, Coro1c is elevated in postmortem brain tissue from PD subjects, where it may impede the protective function of Rab27b. These data suggest that KD or inhibition of Coro1c may be advantageous for elevating lysosomal function in a therapeutic context.

Disclosures: K. Scholz: None. **C. Craig:** None. **L. Matheny:** None. **T.A. Yacoubian:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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NIH T32 Grant 5T32NS095775
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Title: Rab27a as a potential target for therapeutic intervention in Parkinson's Disease

Authors: *M. A. GANNON, K. SCHOLZ, R. SYED, L. MATHENY, A. PETIT, C. CRAIG, T. A. YACOUBIAN;
Neurol., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: In Parkinson's Disease (PD) and other synucleinopathies, toxic alpha-synuclein (asyn) is hypothesized to spread from cell to cell in a prion-like manner. While this propagation likely drives disease, the mechanisms driving the release and uptake of asyn are not fully understood. Our lab has identified the small GTPase Rab27a as a potential modulator of asyn uptake. Rab27a is a small GTPase that is expressed in PD-relevant brain areas, including dopaminergic cells in the substantia nigra pars compacta (SNpC). While we have previously shown that knockout (KO) of its sister isoform, Rab27b, results in impaired autophagy and exacerbates asyn pathology, we surprisingly found that Rab27a KO is protective against asyn pathology in hippocampal primary neurons treated with pre-formed asyn fibrils (PFFs). Rab27a KO neurons treated with PFFs accumulate significantly less asyn inclusions positive for S129 phosphorylation (pS129) than WT controls at 7, 10, and 14 days after PFF treatment. Since Rab27a is known to promote endocytosis in pancreatic beta cells, we hypothesized that it may also promote endocytosis in neurons. Thus, the loss of Rab27a may impair the endocytosis and propagation of PFFs and thereby ameliorate downstream asyn pathology. We have found that Rab27a KO in primary neurons reduces the endocytosis of Alexa 488-labeled dextran, and preliminary data suggest it similarly reduces the uptake of asyn PFFs. To assess the role of Rab27a *in vivo*, we injected PFFs unilaterally into the striatum of Rab27a KO and WT mice and collected tissue at 6 weeks, 8 weeks, and 6 months post injection (mpi) to assess the development of pathology, including asyn inclusion formation and dopaminergic cell loss over time. Our preliminary data indicate that Rab27a KO may slow the onset of PFF-related pathology, delaying the trajectory of asyn inclusion formation and protecting against DA cell loss. Our findings so far have highlighted Rab27a as a potential target for therapeutic intervention in PD.

Disclosures: M.A. Gannon: None. **K. Scholz:** None. **R. Syed:** None. **L. Matheny:** None. **A. Petit:** None. **C. Craig:** None. **T.A. Yacoubian:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Topic: C.03. Parkinson's Disease

Support: NIH Grant RF1-NS136240
NIH Grant F31-ES034986

Title: Disruption of 14-3-3 Protein-Protein Interactions Results in Mitochondrial Dysfunction

Authors: *C. CRAIG, T. A. YACOUBIAN;
Neurol., Univ. of Alabama at Birmingham, BIRMINGHAM, AL

Abstract: Functional mitochondria are key for brain health, but as the population ages, so too do the powerhouses. While mitochondria damage is well characterized in aging and several neurodegenerative diseases, the catalyst of this transition from healthy to dysfunctional is still

unclear. One potential player is the diverse family of 14-3-3 proteins, modulating cellular functions through protein-protein interactions (PPIs). Our group previously found a dramatic increase in 14-3-3θ phosphorylation in human Parkinson's Disease (PD), Alzheimer's Disease (AD), and Dementia with Lewy bodies (DLB) brains compared to healthy controls. Mechanistically, we also found 14-3-3θ phosphorylation at S232 disrupts many key PPIs involved in vesicular transport, like NDEL1, as well as cellular respiration, like hexokinase and pyruvate dehydrogenase. To begin to elucidate the effects of PPI interference on mitochondria, we used difopein, a pan 14-3-3 inhibitor that competitively blocks the binding pocket. Using primary neuronal cultures expressing difopein in the hippocampus and cortex, we found modest defects in retrograde trafficking of mitochondria with more pausing of mitochondria along the axon as well as diminished mitochondria membrane potential. In an α-synuclein overexpressing cell model, we similarly found that 14-3-3 inhibition caused a 30% reduction in mitochondrial membrane potential as well as a 31% and 52% reduction in basal and maximal respiration rates, respectively. To study the PPIs more specifically disrupted in disease, we developed novel knock-in genetic mouse models of 14-3-3θ phosphorylation (S232D) and its nonphosphorylatable control (S232A). Using primary neuronal cultures from S232D/A mice to investigate the effects of S232 phosphorylation on mitochondrial respiration and health revealed a 31% reduction of membrane potential in S232D neurons compared to Cre control neurons, while S232A neurons maintained stably polarized mitochondria. Mitochondrial numbers were no different in either S232A or S232D neurons compared to Cre controls as measured by TOMM20 intensity. Future experiments will utilize Seahorse Bioanalysis to study respiration rates and the differential effects of upstream binding to hexokinase and pyruvate dehydrogenase on metabolism efficiency in neurons expressing S232 phospho-mutants.

Disclosures: C. Craig: None. **T.A. Yacoubian:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Program #/Poster #: PSTR305.11/V12

Topic:

Support: NIEHS Grant R01ES034846
NIH Grant 5T32NS061788-18

Title: Lysosomal dysfunction as an initiating and persistent mechanism of environmental toxicant-induced Parkinson's neurodegeneration

Authors: *T. WALTERS[1], N. ILIEVA[2], K. SCHOLZ[3], A. ADAMSON[4], K. L. ESKOW JAUNARAJS[5], A. I. BERNSTEIN[6], B. R. DE MIRANDA[7];
[1]The Univ. of Alabama at Birmingham, Birmingham, AL; [2]Neurol., Univ. of Alabama, Birmingham, Birmingham, AL; [3]Univ. of Alabama At Birmingham, Birmingham, AL; [4]Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [5]Univ. of Alabama at Birmingham,

Springville, AL; [6]Pharmacol. and Toxicology, Rutgers Univ., Piscataway, NJ; [7]Neurol., UAB, Birmingham, AL

Abstract: Environmental exposures increase Parkinson's disease (PD) risk by initiating neurotoxic pathways that result in neurodegeneration. We and others have previously shown that exposure to industrial byproducts, like the organic solvent trichloroethylene (TCE), induces neurotoxicity within the dopaminergic system and recapitulates hallmark PD pathology, such as alpha-synuclein aggregation, oxidative stress, and endolysosomal dysfunction in adult rodents. Mitochondrial dysfunction has been postulated as a central component of toxicant-induced PD, and while the bioenergetic dysfunction initiated by mitochondria can instigate neurotoxic pathways, the loss of lysosomal activation as a result may play a more integral role in the sustained and persistent neuropathology that drives disease phenotype from environmental risk factors. To assess initiating neurotoxic changes that occur before neuron loss, we exposed adult, wildtype mice to 100 ppm TCE for 4 weeks and measured a significant reduction of cathepsin D within dopaminergic neurons ($p<0.0001$), and elevated accumulation of lysosomal degradation products within neurons (SCMAS; $p<0.0001$). To assess more sensitive measures of TCE-induced neurotoxicity before neurodegeneration, adult, wildtype mice were exposed to 100 ppm of TCE for 6 weeks, and their ventral midbrains were collected for snRNA-seq. Mice that were exposed to both models of pre-degenerative TCE exposure displayed a significant dysregulation in genes related to lysosomal activity, particularly related to lysosomal acidification factors in neuronal and non-neuronal cell types. This effect indicates that toxicant-induced lysosomal dysfunction may be a key factor in both initiating and sustaining persistent neurotoxicity in the context of PD risk across the lifespan.

Disclosures: T. Walters: None. **N. Ilieva:** None. **K. Scholz:** None. **A. Adamson:** None. **K.L. Eskow Jaunarajs:** None. **A.I. Bernstein:** None. **B.R. De Miranda:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.12/V13

Topic: C.03. Parkinson's Disease

Title: PAK6 promotes neuronal autophagy via TFEB activation.

Authors: *F. AGOSTINI, M. BISAGLIA, N. PLOTEGHER, E. GREGGIO;
Univ. of Padova, Padova, Italy

Abstract: Autophagy impairment is a common hallmark of neurodegenerative disorders. The link between defective autophagic clearance and neurodegeneration was first demonstrated over two decades ago in autophagy-deficient mouse models, and since then autophagic dysfunction has been extensively investigated in neurodegenerative diseases. Although autophagy activation is considered a therapeutic approach in neurodegeneration, its differential regulation across cell

types poses a major challenge for achieving neuron-specific interventions. In this project, we identified and characterized the neuronal-enriched p21-activated kinase 6 (PAK6) as a positive regulator of autophagy in neuronal cells. Using biochemical approaches and imaging techniques, we investigated the role of PAK6 in both *in vivo* and *in vitro* models. Specifically, we employed Parkinson's disease (PD) *Drosophila melanogaster* and mouse models to study the effects of PAK6 on neuronal autophagy, while Hela cells were used to mechanistically understand PAK6-mediated autophagy regulation. In *Drosophila melanogaster*, neuronal downregulation of the PAK6 ortholog mushroom bodies tiny (mbt) resulted in autophagic defects, including reduced lysosome number and decreased lysosomal activity in the brain. Moreover, mbt silencing in dopaminergic neurons promoted neuronal loss and α-synuclein aggregation. Consistent with these findings, overexpression of a constitutively active form of PAK6 in a PD mouse model reduced α-synuclein levels in dopaminergic neurons. To elucidate the underlying molecular mechanism, we overexpressed wild-type and constitutively active PAK6 in HeLa cells and found that PAK6 activity strongly promotes the nuclear translocation of transcription factor EB (TFEB), the master transcriptional regulator of autophagy and lysosomal biogenesis. Given the established role of 14-3-3 proteins as TFEB inhibitors and their known phosphorylation by PAK6, we investigated the interactions among these proteins. Proximity ligation assays and fluorescence correlation analyses demonstrated that active PAK6 interacts with both TFEB and 14-3-3 proteins, promoting the formation of a tri-protein complex that facilitates TFEB nuclear localization.Collectively, our findings identify PAK6 as a novel activator of TFEB-dependent autophagy in neurons, highlighting its potential role as target for the selective modulation of neuronal autophagy.

Disclosures: F. Agostini: None. **M. Bisaglia:** None. **N. Plotegher:** None. **E. Greggio:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.13/V14

Topic: C.03. Parkinson's Disease

Title: Disruption of VPS13C mediated mitochondrial homeostasis in experimental models of Parkinson's disease

Authors: *S. ASMI T[1], G. CHANDRA[2];
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Abstract: Vacuolar protein sorting 13 homolog C (VPS13C) is a lipid transfer protein that mediates non-vesicular lipid transport at organelle contact sites and is genetically linked to autosomal recessive Parkinson's disease (PD). Although mitochondrial dysfunction is a central

feature of PD pathogenesis, the relationship between VPS13C and mitochondria remains poorly understood. We therefore investigated the mitochondrial association of VPS13C and its response to Parkinsonian stress. To address this, immunofluorescence imaging, subcellular fractionation, western blotting, siRNA-mediated gene silencing, reactive oxygen species assays, and rotenone-induced cellular and animal models of PD were employed. Immunofluorescence analysis in retinoic acid-differentiated SH-SY5Y cells demonstrated extensive co-localization of VPS13C with MitoTracker-labeled mitochondria and the mitochondrial outer membrane protein TOM70 (n=150 cells). Cellular fractionation followed by western blotting further confirmed the presence of VPS13C in the mitochondrial fractions. To determine the functional significance of VPS13C, siRNA-mediated knockdown was performed in SH-SY5Y cells, resulting in marked mitochondrial fragmentation and increased reactive oxygen species generation (n = 150 cells each). To examine whether VPS13C is altered during PD-associated stress, rotenone-induced cellular and animal models were established. Time response analyses in SH-SY5Y cells using 1 μM rotenone for 7 days demonstrated a reduction in VPS13C protein expression with prolonged rotenone exposure. Consistent with the cellular findings, chronic rotenone exposure (2 mg/kg, s.c., 18 d) in male Sprague-Dawley rats led to a significant decrease in VPS13C protein expression within the ventral midbrain. Together, these findings identify VPS13C as a mitochondria-associated protein that is essential for maintaining mitochondrial integrity and is selectively depleted during Parkinsonian stress. These results implicate VPS13C dysfunction as a potential contributor to mitochondrial pathology in PD and provide a foundation for investigating the mechanisms linking VPS13C dysregulation to neurodegeneration.

Disclosures: S. Asmi T: None. **G. Chandra:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.14/V15

Topic: C.03. Parkinson’s Disease

Support: ASAP-000458

Title: Evaluating the cleavage and processing of GPNMB

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[1]Med. Genet. Br., Natl. Human Genome Res. Inst., Bethesda, MD; [2]NHGRI, NIH, Bethesda, MD

Abstract: Lysosomal storage disorders (LSDs) are characterized by lysosomal dysfunction, and understanding their cell biology has broad implications for neurodegeneration. Gaucher disease (GD), caused by biallelic pathogenic variants in *GBA1* encoding glucocerebrosidase (GCase), leads to lysosomal lipid accumulation. *GBA1* variants are also the most common genetic risk factor for Parkinson disease (PD), yet the mechanistic link remains unclear. We investigated glycoprotein nonmetastatic melanoma B (GPNMB), a transmembrane protein whose cleaved N-

terminal ectodomain (ECD) is elevated in the cerebrospinal fluid of GD and PD patients and has been shown to bind alpha-synuclein and facilitate its neuronal uptake. Despite therapeutic interest, the cleavage products and intracellular trafficking of GPNMB remain poorly defined. To address this gap, we engineered an H4 glioma cell line stably expressing dual-tagged GPNMB. Live-cell imaging revealed spatial separation of the termini at steady state, with the N-terminus enriched in lysosomes, which is consistent with a novel 12-kDa N-terminal fragment (B4) identified in iPSC-derived dopaminergic neurons. Pulse-chase experiments further showed that GPNMB termini co-localize in early endosomes before separating at around 12 hours, suggesting cleavage occurs in endosomes prior to plasma membrane delivery. Finally, immunoprecipitation of N-terminal GPNMB from conditioned media identified the full-length ECD alongside smaller secreted fragments, revealing complexity in ECD processing. Ongoing mass spectrometry efforts aim to define the precise peptide sequences of these fragments, with implications for therapeutically targeting GPNMB in GD and PD. Preliminary results will be validated in disease-relevant iPSC-derived microglia models.

Disclosures: S. Das: None. **Y. Chen:** None. **E. Sidransky:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Program #/Poster #: PSTR305.15/V16

Topic: C.03. Parkinson’s Disease

Support: APDA-Research Grant

Title: Characterization of GPNMB intracellular localization and extracellular release in cell lines and induced pluripotent stem cell derived dopaminergic neurons under lysosomal dysfunction

Authors: *M. H. MONJE[1], G. MINAKAKI[1], N. SAFREN[1], R. COUKOS[1], Y. ZHOU[1], D. KRAINC[2];
[2]Dept Neurol., [1]Northwestern Univ., Chicago, IL

Abstract: Glycoprotein non-metastatic melanoma protein B (GPNMB) is a transmembrane glycoprotein implicated in Parkinson's disease (PD). Increased GPNMB expression is associated with increased PD risk (PMID: 25064009; PMID: 35981040), and elevated GPNMB levels have been found in the plasma of individuals with PD regardless of genetic status (PMID: 37497669; PMID: 40594632). Moreover, it has been proposed that endolysosomal dysfunction, a key PD pathomechanism, increases GPNMB levels and promotes extracellular release of the protein (PMID: 41406229). These findings suggest that extracellular GPNMB levels could serve as a valuable biomarker for lysosomal function in PD.Our study aims to evaluate extracellular GPNMB as a biomarker of lysosomal function in neuronal cells. To this end, we examine GPNMB localization and interaction with the endolysosomal compartment in cell lines and induced pluripotent stem cell-derived dopaminergic neurons from control or individuals with

GBA1-PD. Furthermore, we investigate the impact of lysosomal dysfunction on GPNMB release in a free form or in association with exosomes/extracellular vesicles (EVs). Using immunofluorescence and live cell imaging in HeLa cells stably expressing HA-tagged GPNMB, we found that GPNMB is predominately localized on LAMP1+ endolysosomes both under baseline and upon pharmacologically induced lysosomal stress (chloroquine). Moreover, in dopaminergic neurons endogenous GPNMB was also enriched in endolysosomes. In both cellular models, lysosomal stress increased GPNMB on endolysosomes and was accompanied by increased release, partly associated with EVs. Ongoing studies are focused on the quantitative examination of changes in GPNMB protein levels in endolysosomes versus extracellularly released protein under various paradigms of lysosomal dysfunction, in control or *GBA1*-PD dopaminergic neurons, using ELISA.These findings will provide insight into cellular pathways contributing to GPNMB release in neuronal cells under lysosomal stressors, which is relevant to evaluating the potential of GPNMB as a biomarker of lysosomal dysfunction in PD.

Disclosures: M.H. Monje: A. Employment/Salary (full or part-time):; Northwestern Medicine, Northwestern 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.; APDA research grant recipient. **G. Minakaki:** A. Employment/Salary (full or part-time):; Northwestern University. **N. Safren:** A. Employment/Salary (full or part-time):; Northwestern University. **R. Coukos:** A. Employment/Salary (full or part-time):; Northwestern University. **Y. Zhou:** A. Employment/Salary (full or part-time):; Northwestern University. **D. Krainc:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Topic: C.03. Parkinson’s Disease

Support: SECTEI/146/2024

Title: α-Synuclein modulation of $Ca_V1.3$ channels: possible physiological roles and pathological consequences

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Abstract: Voltage-gated calcium channels (Cav) are integral membrane proteins that function as pores through which calcium enters the cell, an event crucial for triggering multiple cellular functions, such as neurotransmitter release. On the other hand, impaired Cav channel function is

commonly associated with various neurological disorders, including Parkinson's disease (PD), where cell death may be related to misfolding and abnormal function of the α-synuclein (α-syn) protein, along with calcium overload in dopaminergic neurons of the substantia nigra pars compacta (SNc) that occurs due to dysregulation of Cav1.3 channel activity. This compromises Ca^{2+} homeostasis, activates cytotoxic events, and accelerates neurodegeneration. This study aims to determine whether α-syn affects channel activity and, if so, whether the mechanism is direct or mediated by a molecular cofactor. To this end, channel activity was evaluated in the HEK-293 cells heterologous expression system, in the presence and absence of α-syn, using the patch-clamp technique in whole-cell mode. The results show that α-syn decreases Cav1.3 channel activity without affecting the kinetic properties of the currents. In silico analysis suggested that the interaction between α-syn and the channels might require an intermediary, such as calmodulin (CaM). To test this hypothesis, pharmacological inhibition of CaM (with W13) was performed, as well as removal of the CaM binding site in α-syn through site-directed mutagenesis. The results of this analysis show that both the CaM inhibitor and the mutations prevent the effect of α-syn on the currents. Similarly, in a series of parallel experiments, it was found that two α-syn mutations linked to familial PD, A53T and S129D, do not modify the activity or alter the biophysical properties of Cav1.3 channels. Overall, this evidence suggests that physiological α-syn functions as a negative regulator of CaV1.3 channels, critical determinants of dopaminergic neuron pacemaking in the SNc, whereas aggregated α-syn fails to exert such control. Understanding how Cav channel activity is regulated by α-syn will allow establishing the basis to explain how these proteins intervene in the onset and development of PD.

Disclosures: R. Felix: None. **B. Vargas Caballero:** None. **A. Corzo Lopez:** None. **R. Gonzalez-Ramirez:** None. **A. Sandoval:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.17/V18

Topic: C.03. Parkinson’s Disease

Support: NIH Grant 5R01HL162909
OSU Presidential Fellowship
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Title: Neddylation sustains the endolysosomal-mitochondrial axis by stabilizing Rab7 in Parkinson's disease

Authors: *K. CHEN[1], S. CHAUDHURI[2];
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Abstract: Parkinson's disease (PD) features lysosomal dysfunction, mitochondrial damage, and impaired mitophagy (clearance of damaged mitochondria by lysosomes), but the mechanisms that maintain the mitochondria-lysosome quality-control axis in midbrain dopaminergic neurons remain unclear. We investigated whether neddylation, a ubiquitin-like post-translational modification, regulates this axis in dopaminergic neurons. Using proteomic datasets from postmortem substantia nigra tissue of 20 healthy controls and 40 PD patients, we found that the neddylation E1 subunits NEDD8-activating enzyme E1 regulatory subunit 1 (NAE1) and ubiquitin-like modifier activating enzyme 3 (UBA3) were downregulated, accompanied by NEDD8 accumulation at early disease stages, suggesting that impaired neddylation may contribute to the initiation of Parkinson's disease. To determine the functional consequences of neddylation deficiency, we generated dopaminergic neuron-specific NAE1 conditional knockout mice on a C57BL/6J background ($NAE1^{fl/fl}$; Slc6a3-Cre). At P45, NAE1 signal in tyrosine hydroxylase (TH) positive neurons was reduced to 67.6 ± 5.7% of wild-type (WT) levels (mean±SEM; n=3/group; unpaired t-test, p=0.041). By P70, striatal TH-positive projections were reduced from 1.000 ± 0.075 to 0.753 ± 0.042, accompanied by motor deficits in rotarod and pole tests. Mechanistically, NEDD8 modification stabilized Rab7 at K194 and facilitated Rab7 membrane cycling by promoting its dissociation from late endosomal and lysosomal membranes. NAE1 loss promoted lysosomal degradation of Rab7, resulting in impaired endosome-lysosome maturation, reduced lysosomal acidification, and abnormal lysosomal accumulation. Reduced Rab7 also weakened lysosome-mitochondria interactions and decreased mitophagy flux measured by mt-Keima in primary cortical neurons. Consistently, NAE1-knockout SH-SY5Y cells exhibited mitochondrial depolarization and impaired respiration as assessed by TMRM and Seahorse analyses. Notably, pharmacological activation of TRPML1 with ML-SA5 restored Rab7 levels, improved lysosomal biogenesis and acidification, enhanced mitophagy, and rescued organelle function. Together, these findings identify NAE1-dependent neddylation as an upstream protective mechanism that maintains Rab7-dependent endolysosomal-mitochondrial quality control and suggest TRPML1 activation as a potential bypass strategy for mitochondria-lysosome dysfunction in PD.

Disclosures: K. Chen: None. **S. chaudhuri:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.18/V19

Topic: C.03. Parkinson’s Disease

Title: Role of the retromer component VPS35 as a critical regulator of mitochondrial dynamics in Parkinson's disease.

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Abstract: Mitochondrial dysfunction, including disrupted mitochondrial dynamics, is a hallmark of neurodegenerative disorders, including Parkinson's disease (PD). A PD-associated VPS35 mutant has been reported to cause mitochondrial defects and impair mitophagy. Still, the role of this retromer in the trafficking of mitochondrial fusion (MFN1/2, OPA1) and fission (dynamin-related protein 1 (DRP1), proteins is not clear. Although VPS35 has emerged as a critical regulator of endosomal trafficking, the molecular mechanisms linking VPS35 to mitochondrial fission machinery remain incompletely understood. Here, we investigated the role of VPS35 in co-ordinating mitochondrial protein trafficking using VPS35 siRNA-mediated silencing, Fluorescence microscopy, Co-IP, Western blotting, and bioinformatics tools. We have shown that VPS35 siRNA-induced mitochondrial fragmentation is DRP-1 dependent and VPS35 is required for the retrieval of DRP1 from mitochondria. VPS35 protein was transiently silenced by knockdown, and mitochondrial morphology was assessed by fluorescence microscopy. VPS35-deficient cells exhibited a significant increase in fragmented mitochondria compared with control cells, indicating impaired mitochondrial network integrity. To determine whether the observed fragmentation was DRP1-dependent, cells were treated with a selective DRP1 inhibitor, Mdivi-1. This pharmacological inhibition of DRP1 significantly rescued mitochondrial fragmentation in VPS35-knockdown cells, suggesting that the observed fragmentation is DRP1-dependent. Interestingly, mitochondrial fractionation studies showed increased accumulation of DRP1 in mitochondria in VPS35-deficient cells compared with controls, suggesting VPS35 is required for the retrieval of DRP1 from mitochondria. To determine whether VPS35 interacts with DRP1, co-immunoprecipitation experiments were performed and revealed interaction between endogenous VPS35 and DRP1. To explore the structural basis of this interaction, protein-protein docking analyses were conducted and found that DRP1 binds to the C-terminal region of VPS35, which contains the established cargo-binding domains of the retromer complex. Taken together, these findings suggest that VPS35 is required for the removal of DRP1 from mitochondria following fission events. Loss of VPS35 leads to mitochondrial retention of DRP1, resulting in excessive fission and mitochondrial fragmentation. Our research findings establish a mechanistic link between retromer dysfunction and aberrant mitochondrial dynamics and reveal a potential therapeutic target for diseases associated with VPS35 deficiency.

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

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.19/V20

Topic: C.03. Parkinson's Disease

Title: Characterization of hexokinase 3 deficiency in Parkinson's disease associated pathways

Authors: *A. DROZMAN[1], T. MALANKHANOVA[1], A. B. WEST[2];
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Abstract: Hexokinase 3 (HK3) is a glycolytic enzyme that catalyzes the phosphorylation of glucose to glucose-6-phosphate, a rate-limiting step in glycolysis and cellular energy metabolism. HK3 is selectively enriched in myeloid cells and is strongly induced during monocyte-to-macrophage differentiation, suggesting a specialized role in myeloid immunometabolism. However, the mechanisms by which HK3 influences inflammatory signaling, lysosomal biology, and disease-relevant transcriptional programs in myeloid cells remain poorly understood.

To investigate HK3 function, we generated HK3-deficient human THP-1 monocytic cells using CRISPR/Cas9-mediated gene editing. Successful disruption of HK3 was confirmed by Sanger sequencing and western blot analysis. Bulk RNA sequencing revealed suppression of interferon-α and interferon-γ response pathways, together with enrichment of MYC target gene signatures, suggesting that loss of HK3 shifts the transcriptional state of THP-1 cells toward reduced interferon signaling and increased proliferative programs. HK3-deficient cells also showed altered expression of several genes associated with Parkinson's disease and mitochondrial quality control, including increased LRRK2, PRKN, and SNCA expression and reduced PINK1 expression. These changes suggest that HK3 loss may perturb pathways related to mitochondrial stress responses and neurodegeneration-associated gene regulation. In addition, reduced expression of TYROBP, a myeloid immune signaling adaptor linked to neurodegenerative disease risk, further supports a broader disruption of innate immune signaling in HK3-deficient cells.

Functional characterization using LysoSensor Green staining and flow cytometry demonstrated increased lysosomal fluorescence intensity in HK3-deficient cells compared with wild-type controls, consistent with altered lysosomal physiology. Notably, HK1 and HK2 expression were not compensatorily increased, supporting a non-redundant role for HK3 in human myeloid cells. Together, these findings establish HK3 as an unexpected regulator of myeloid immunometabolism, with effects on interferon signaling, lysosomal function, and neurodegeneration-associated transcriptional programs. Ongoing studies will determine whether HK3-dependent changes functionally intersect with LRRK2 kinase activity and alter myeloid responses to pathological stimuli such as aggregated α-synuclein.

Disclosures: A. Drozman: None. **T. Malankhanova:** None. **A.B. West:** None.

Poster

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Topic: C.03. Parkinson's Disease

Support: NINDS Grant 1ZIANS003135-12
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Title: Axonal function is impaired early in a mouse model of progressive parkinsonism

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Abstract: Parkinson's disease is caused by the death of dopamine-producing neurons in the substantia nigra pars compacta (SNc). It is hypothesized that the death of the nigrostriatal axons of these neurons precedes and contributes to cell death in the SNc. In support of this hypothesis, loss of striatal dopaminergic fibers occurs before SNc cell death in a mouse model of progressive parkinsonism resulting from mitochondrial dysfunction, the MitoPark model. Striatal dopamine release is also decreased before striatal fiber loss in this model, suggesting that impairments in axonal function may be present before axonal degeneration. Here, we explore if axonal function is impaired before the onset of axon loss in the MitoPark mouse model of Parkinson's disease. To determine if deficits in axonal function precede axon loss, we performed calcium imaging and electrophysiological recordings in the axons of MitoPark mice and age-matched controls at several timepoints preceding SNc cell death and striatal fiber loss (6 weeks, 9 weeks, and 12 weeks of age). We examined both the ability of striatal axons to follow evoked high-frequency activity (20 Hz and 100 Hz) as well as their ability to propagate signals down highly-branching axonal arbors. We measured calcium signals both using bulk slice photometry and two-photon microscopy to determine calcium signals in single dopaminergic axons. We found a reduction in stimulation-evoked calcium signals after 9 weeks of age in MitoPark but not control mice, suggestive of an impairment in nigrostriatal axonal function that begins before the overt loss of dopaminergic fibers. Additionally, we found that propagation is impaired in MitoPark axons relative to controls at this age, implying changes in excitability occur before axonal death. Understanding how axonal signaling is changed before axon die-back and neuronal death may illuminate new strategies to prolong the survival of axons and prevent the death of SNc dopamine neurons in the face of energetic challenges.

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Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Topic: C.03. Parkinson's Disease

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Title: Regulator of G-protein Signaling 6 (RGS6) Controls Dopamine Reuptake via the Dopamine Transporter (DAT) in Nigrostriatal Dopamine Neurons

Authors: *D. LIU[1,2,3], J. YANG[2], D. LI[2], M. GUO[2], N. FASSETT[2], J. BERNHOLTZ[2], R. A. FISHER[2], A. STEWART[2];

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Abstract: Parkinson's disease (PD) is one of the most common and debilitating neurodegenerative diseases, and its prevalence continues to climb globally. Although dopamine (DA)-restoring therapies can alleviate motor symptoms, no disease-modifying treatment for PD is currently available. Therefore, delineating pathogenic drivers of PD is crucial for the identification of novel treatment targets. Our previous study found that expression of regulator of G protein signaling 6 (RGS6) is diminished in dopamine neurons of the substantia nigra pars compacta (SNc) from postmortem PD brains. In establishing if RGS6 loss is causative in PD pathogenesis, we determined that RGS6-/- mice exhibit age-dependent loss of tyrosine hydroxylase + (TH+) DA neurons, disruptions in DA metabolism, α-synuclein aggregation, and motor coordination deficits. DA neurotransmission is dynamically controlled by the actions of D2 autoreceptors (D2ARs), which suppress neuronal firing, inhibit vesicular release, and facilitate DA reuptake via the dopamine transporter (DAT). *Rgs6*, *Drd2*, and *Slc6a3* expression are enriched in DA neurons of the SNc relative to the ventral tegmental area (VTA), and RGS6 canonically functions to limit the signaling response to Gαi/o-coupled receptors (GPCRs), including D2ARs. Here, we demonstrate that uptake of [^{3}H]DA is elevated selectively in the dorsal striatum (DStr) of male RGS6-/- mice, a phenotype absent in females. DStr DA uptake is also insensitive to quinpirole, a D2R agonist, in the absence of RGS6. To test if DAT activity is altered in RGS6 knockouts in vivo, we injected the oxidation-prone DA analog 6-hydroxydopamine (6-OHDA), a DAT substrate, into the SNc of RGS6-/- mice. As expected, loss of RGS6 sensitized mice to the deleterious impacts of 6-OHDA, including disrupted DA metabolism, DA depletion, and motor coordination deficits. RGS6 and DAT also form a co-precipitable complex in a heterologous expression system, and ongoing work seeks to determine if the ability of RGS6 to block DAT function requires RGS6's GTPase-activating protein (GAP) function and D2AR regulatory capacity. We further seek to establish the role of RGS6-dependent DAT regulation in DA neuron degeneration as well as *in vivo* DA dynamics and behavior as a function of both age and biological sex.

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Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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Topic: C.03. Parkinson's Disease

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NFS I-Corp Program
The Center for Development and Behavioral Neuroscience at Binghamton University

Title: Role of dorsal raphe nucleus vesicular glutamate transporter 3 possession in regulating striatal neurotransmission and dyskinetic behaviors in a rat model of levodopa-induced dyskinesia

Authors: *C. BUDROW[1], I. M. SANDOVAL[2], W. GAO[3], G. VAUGHAN[1], L. BERNAL CONDE[3], A. KARKHANIS[4], F. P. MANFREDSSON[2], C. R. BISHOP[5];
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Abstract: Parkinson's disease (PD) is a neurodegenerative movement disorder marked by progressive cell death of nigral-originating dopamine (DA) neurons. Although levodopa (L-DOPA) remains the gold-standard treatment for motor symptoms, chronic administration frequently leads to L-DOPA-induced dyskinesia (LID), a debilitating complication typified by abnormal involuntary movements (AIMs) and dystonia. Maladaptive neuroplasticity of the raphe-striatal serotonin (5-HT) system is a key factor in LID. Interestingly, emerging evidence has revealed a propensity for dorsal raphe nucleus (DRN) 5-HT neurons to co-package/release glutamate (GLU) via vesicular GLU transporter 3 (VGLUT3), suggesting a novel convergence and unexplored mechanism of 5-HT circuitry contributing to LID. The present studies assess the relationship between DRN-5-HT neuronal VGLUT3 content and behavioral and neurochemical correlates of LID. TPH2-Cre+ Long Evans rats (N = 65, 38 M, 27 F) received unilateral 6-hydroxydopamine lesions to the medial forebrain bundle, followed by DRN-targeted VGLUT3 knockdown (KD; AAV9-FlexUTR2-rVGLUT3-miRNA999) or control scrambled miRNA (AAV9-SCR) viral infusions. Following recovery, animals underwent chronic L-DOPA administration (6 mg/kg, s.c.) for 14 days, during which AIMs were assessed. In one group of rats (N = 17, 9 M, 8 F), *in vivo* microdialysis was employed to measure treatment-induced changes in extracellular DA and GLU concentrations. A separate group of animals (N = 48; 29 M, 19 F) underwent post-treatment *ex vivo* fast-scan cyclic voltammetry (FSCV) to examine alterations in striatal DA and 5-HT release dynamics following phasic stimulation. Behaviorally, VGLUT3 KD exacerbated the trajectory and severity of LID, supporting a previously unrecognized modulatory role in LID. Neurochemically, VGLUT3 KD altered striatal DA and GLU concentrations following L-DOPA administration, suggesting disruption of coordinated neurotransmitter signaling within the raphe-striatal circuit. Ongoing FSCV and postmortem analyses will further characterize the impact of VGLUT3 loss on monoamine release kinetics and lesion status. Collectively, these findings support a complex interaction in neurotransmitter signaling in the dyskinetic brain, dependent on shared protein interactions, underscoring the intricacy of 5-HT hyperconnectivity as a mode of maladaptive compensation in LID.

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Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

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A*STAR National Science Scholarship (BS-PhD) to M.P.
V.G. is an Investigator of the Howard Hughes Medical Institute

Title: Molecularly-guided spatial proteomics to understand single-cell-level biology in Parkinson's disease

Authors: *S. DUTTA, M. PANG, G. M. COUGHLIN, S. GUDAVALLI, M. ROUKES, T.-F. CHOU, V. GRADINARU;
Caltech, Pasadena, CA

Abstract: Single-cell spatial proteomics (scSP) holds substantial potential for profiling healthy and diseased tissues. Here, we optimize and apply unbiased scSP to the healthy and diseased mammalian brain, using molecularly-guided laser capture microdissection and unbiased mass spectrometry. We systematically evaluate the effects of tissue fixation, marker staining, and sample input size on proteome coverage and quantitative accuracy. We benchmark this workflow by profiling region-specific neuronal proteomes and describing the response of non-neuronal cells to acute brain injury. Across these applications, we integrate complementary transcriptomic resources to evaluate cross-modality trends and refine neuronal proteomic results by filtering out protein signals likely arising from non-neuronal cells, an essential consideration in heterogeneous tissues such as the brain. Finally, we leverage this approach to resolve proteomic differences between dopaminergic neuron subpopulations with differential vulnerability to Parkinson’s disease and to uncover disease-specific disruptions in α-synuclein-aggregate-bearing cortical neurons from LBD patients and the PFF-injected mouse models of PD. Findings from the PD samples point towards potential alterations in proteasomal and ribosomal pathways. Together, these data demonstrate the utility of scSP in neuroscience research for understanding fundamental biology and the molecular drivers of neurological conditions such as PD.

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Poster

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Topic: C.03. Parkinson’s Disease

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Title: The impact of ATP10B, a GlcCer transporter, on GBA1-associated Parkinson disease in a murine model

Authors: *M. BHATTIPROLU, T. CHEN, B. BERHE, T.-U. HAN, E. SIDRANSKY; Med. Genet. Br., Natl. Human Genome Res. Institute, Natl. Inst. of Hlth., Bethesda, MD

Abstract: Introduction: Mutations in *GBA1*, which encodes the lysosomal enzyme glucocerebrosidase (GCase), result in the accumulation of the lipid substrates glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph). *GBA1* variants are also among the most common genetic risk factors for Parkinson's disease (PD). ATP10B is a late endolysosomal GlcCer flippase, and loss-of-function variants in *ATP10B* have been associated with increased PD risk. Both proteins regulate glycosphingolipid homeostasis through related lysosomal pathways, suggesting they might both contribute to the development of *GBA1*-associated PD in a synergistical manner. **Methods:** A murine model was used to evaluate the potential synergistic effect of both decreased GCase activity and loss of *ATP10B* on PD pathology. An *Atp10b* knockout (*Atp10b*$^{-/-}$) mouse model was generated using the CRISPR/Cas9 system. GCase deficiency was induced by daily intraperitoneal administration of the GCase inhibitor conduritol-β-epoxide (CBE) for 28 days in 3-month-old wild-type (WT) and *Atp10b*$^{-/-}$ mice. Two CBE doses were evaluated (50 and 100 mg/kg body weight). Behavioral and biochemical analyses were performed to assess PD-related phenotypes. **Results:** GlcCer levels were elevated in high dose (100 mg/kg) CBE-treated *Atp10b*$^{-/-}$ mice compared with untreated WT, untreated *Atp10b*$^{-/-}$, and high dose CBE-treated WT mice. GlcSph levels increased dramatically in CBE-treated mice in a dose-dependent manner. However, no significant difference in GlcSph levels was observed between CBE-treated *Atp10b*$^{-/-}$ and WT mice. WT and *Atp10b*$^{-/-}$ mice receiving high-dose CBE developed pronounced motor deficits and rapid weight loss. Markers of neuroinflammation and lysosomal stress were increased in all high-dose CBE-treated groups relative to untreated controls. However, *ATP10B* deficiency did not worsen inflammatory or lysosomal stress phenotypes following CBE treatment. No significant differences in dopaminergic neuron levels were observed among groups. **Conclusions:** *ATP10B* deficiency combined with pharmacological GCase inhibition increased GlcCer accumulation but did not exacerbate other PD-related pathologies in the groups examined. These findings suggest that GlcCer accumulation alone may not be a critical driver of PD progression. This model may be useful for investigating the contribution of lipid dysregulation on the pathogenesis of *GBA1*-associated PD.

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Poster

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Topic: C.03. Parkinson's Disease

Support: ASAP-000458

Title: ATP10B and GBA1 deficiency in human iPSC-derived neurons reveals lipid accumulation and Parkinsons disease-relevant pathology

Authors: *N. FISHER[1], M. BHATTIPROLU[2], Y. CHEN[2], E. SIDRANSKY[2];
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Abstract: Background: Pathogenic variants in *GBA1*, the gene encoding glucocerebrosidase (GCase), are well established genetic risk factors for Parkinsons disease (PD). GCase is a lysosomal hydrolase whose deficiency leads the accumulation of lipid substrates glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph) and lysosomal dysfunction. ATP10B, a lipid flippase localized at endolysosomal compartments and responsible for the transport of glucosylceramide and phosphatidylcholine from the inner to the outer leaflet, has also been implicated as a PD risk factor. While both genes converge on lysosomal lipid homeostasis, their functional interaction in human neurons remains poorly understood. We investigated the effects of *GBA1* and *ATP10B* deficiency in a human induced pluripotent stem cell (iPSC)-derived neuronal model to determine whether double knockout could exacerbate lysosomal perturbation and PD-relevant cellular phenotypes. **Methods:** Isogenic wild-type, *GBA1* knockout (KO), *ATP10B* KO, and *GBA1/ATP10B* double-KO iPSC lines were differentiated into excitatory cortical-like neurons using a doxycycline-inducible NGN2 protocol. Neurons were matured for 21 days prior to analysis. Lipid accumulation was assessed and α-synuclein expression was evaluated by western blotting. **Results:** *ATP10B* deficiency resulted in increased levels of GlcSph and GlcCer relative to wild-type neurons, while *GBA1* deficiency produced a more pronounced elevation. Notably, *GBA1/ATP10B* double-KO neurons demonstrated the greatest accumulation of GlcSph and GlcCer species, suggesting a synergistic disruption of lysosomal lipid transport and metabolism. Compared to wild-type cells, ATP10B KO neurons exhibited approximately a 40-fold increased in glucosylsphingosine levels, whereas *GBA1* KO and double-KO neurons showed roughly 300-fold and 700-fold increases, respectively. Elevated α-synuclein expression was observed in ATP10B KO neurons and appeared further increased in double-KO neurons, although additional biological replicates are required to confirm this finding. **Conclusions:** The combined loss of *GBA1* and *ATP10B* enhances glycosphingolipid accumulation in induced-neurons, supporting a potential interaction and converging mechanism between these PD-associated genes. These preliminary findings suggest that ATP10B deficiency may exacerbate lipid dysregulation in the context of *GBA1* loss and contribute to α-synuclein-related pathology. Ongoing studies, including rescue experiments, comprehensive lipidomics, and lysosomal functional assays, will further define the mechanistic relationship between ATP10B and *GBA1* in PD pathogenesis.

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Poster

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Title: Patient-Derived iPSC Neurons and Brain Organoids Recapitulate Dysfunctional and Degenerative Features of Parkinson's and Alzheimer's Diseases

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Abstract: Parkinson's disease (PD) is characterized by the progressive degeneration and loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), resulting in major motor symptoms, such as bradykinesia, tremor, and postural instability. In addition, non-motor symptoms, including cognitive impairment and sleep disorders, are frequently observed in PD patients. Alzheimer's disease (AD), the leading cause of dementia, is characterized by cognitive decline, memory loss, and impaired decision-making, largely due to degeneration of hippocampal and cortical neurons as well as glial dysfunction. A major pathological hallmark of both diseases is the accumulation of misfolded proteins: α-synuclein and phospho-α-synuclein, the principal components of Lewy bodies, in PD, and amyloid-β and Tau/phospho-Tau in AD. Therefore, pathological protein aggregation is a common feature of both disorders. To improve our understanding of the mechanisms underlying neurodegeneration and to identify potential therapeutic targets, we generated DA neurons and mesencephalic organoids from human induced pluripotent stem cells (hiPSCs) derived from PD patients carrying either the N370S or L444P GBA1 mutation. In parallel, we generated hippocampal (HP) neurons and HP organoids from hiPSCs derived from AD patients carrying either the APOE4/4 or APOE3/3 genotype. DA neurons carrying either GBA1 mutation and cultured for 90 days accumulated abundant Lewy body-like inclusions, multilamellar bodies, vacuolated Golgi dictyosomes, and autophagosomes. Moreover, N370S neurons exhibited a significant accumulation of α-synuclein and phospho-α-synuclein inclusions in the cell body and dendrites, accompanied by a significant increase in neuronal firing rate. The contribution of APOE4 to HP neuron neurodegeneration was supported by changes in the levels of amyloid-β42/40, total Tau, and phosphorylated Tau in the culture

medium, as well as by the presence of a greater number of amyloid-β plaques and p-Tau181 aggregates in the cultures. These findings demonstrate that our human-derived cellular models recapitulate key pathological features of neurodegeneration and provide a valuable platform for studying disease mechanisms in PD and AD.

Disclosures: E. Rodríguez Traver: None. **C. Crespo:** None. **R. Vecino:** None. **L. Suárez:** None. **E. Diaz Guerra:** None. **A. Ruiz Laza:** None. **R. Moratalla:** None. **C. Vicario:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.27/V28

Topic: C.03. Parkinson’s Disease

Support: This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (Grant No. RS-2025-02305525)

Title: Marmoset Brain-Derived Neural Stem Cells Model MPP+Induced Mitochondrial Stress and Mitophagy Remodeling

Authors: M. HEO[1], S.-M. KIM[1], K.-S. LEE[2], E. HONG[3], ***H. LEE**[1];
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Abstract: Non-human primate neural stem cell models are needed to bridge the translational gap between rodent neurotoxicology and human neurodegenerative disease. Here, we established a marmoset brain-derived neural stem cell platform and examined its early molecular response to 1-methyl-4-phenylpyridinium (MPP+), a mitochondrial complex I toxin widely used to model Parkinsonian stress. Marmoset neural stem cells were characterized by morphology, immunocytochemistry, and RT-PCR-based lineage profiling, showing neural progenitor-associated expression including Nestin, Vimentin, and Musashi-1, together with additional neural lineage markers. Cells were seeded on poly-D-lysine-coated 35 mm dishes at 2 × 10^5 cells/dish and exposed to MPP+ at 550 or 1100 μM for 6, 12, 24, or 48 h. Untreated cells served as controls. Phase-contrast imaging demonstrated progressive morphological deterioration, most prominently after 1100 μM MPP+ for 48 h. Semi-quantitative RT-PCR analysis of a 30-gene panel revealed coordinated alterations in mitochondrial regulation, mitophagy, apoptosis-related signaling, and oxidative stress defense. Mitochondrial regulatory genes, including PGC-1α, TFAM, NRF1, AMPK, and SIRT1, showed time- and dose-dependent disruption. Mitophagy-associated genes, including PINK1, PRKN, OPTN, AMBRA1, and BNIP3L, display pathway-level remodeling rather than uniform activation, suggesting an imbalanced mitochondrial quality-control response. Cell death-associated transcripts showed complex temporal regulation, including altered BAX/BCL2 balance, modulation of caspase-associated genes, and marked

induction of ATF3 and DDIT3. Oxidative defense genes, including NFE2L2, KEAP1, GPX4, SOD2, FOXO3, NQO1, and CAT, were also altered after prolonged exposure. These findings support marmoset neural stem cells as a translational non-human primate platform for modeling MPP^+-induced mitochondrial stress, mitophagy remodeling, and stress-associated cell death. This early-stage in vitro system may be useful for investigating mechanisms relevant to Parkinsonian neurodegeneration and neuroprotective intervention.

Disclosures: M. Heo: None. **S. Kim:** None. **K. Lee:** None. **E. Hong:** None. **H. Lee:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR305.29/W2

Topic: C.03. Parkinson’s Disease

Support: National Natural Science Foundation of China [82501502]
National Science and Technology Major Project for Brain Science and Brain-like Intelligence Technology[U23A20425]

Title: Single-nucleus transcriptomics of human prefrontal cortex in Parkinson’s Disease reveals cell type-specific state

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Abstract: Parkinson's disease (PD) is a prevalent neurodegenerative disorder, yet cell-type-specific molecular pathology in the living human prefrontal cortex (PFC) remains poorly characterized. We performed single-nucleus RNA sequencing on fresh surgical biopsies of dorsolateral PFC from 11 sporadic PD patients (4F/7M; mean age 66.4) undergoing deep brain stimulation and 7 normal pressure hydrocephalus controls (2F/5M; mean age 69.7). After stringent quality control and MNN integration, we profiled 118,208 nuclei across a three-tier annotation hierarchy encompassing 8 major cell types and 16 neuronal and glial subclasses. Oligodendrocytes increased (52% vs 24%) and astrocytes decreased (12% vs 25%) in PD. PV GABAergic interneurons were selectively expanded (30% vs 22%, p=0.029), while L2/3-CUX2 glutamatergic neurons trended toward reduction (41% vs 63%), with 2,127 and 566 differentially expressed genes identified, respectively, converging on synaptic signaling and neuronal projection pathways.
SCENIC analysis revealed downregulation of ATF2 and RUNX1 regulons and upregulation of ZNF316 and SMAD3 in PD L2/3-CUX2 neurons. CellChat analysis uncovered substantial perturbation of ANGPT and SEMA3 signaling, with SEMA3-mediated excitatory connectivity from L2/3-CUX2 to other glutamatergic subtypes markedly reduced in PD, suggesting disrupted excitation-inhibition balance.

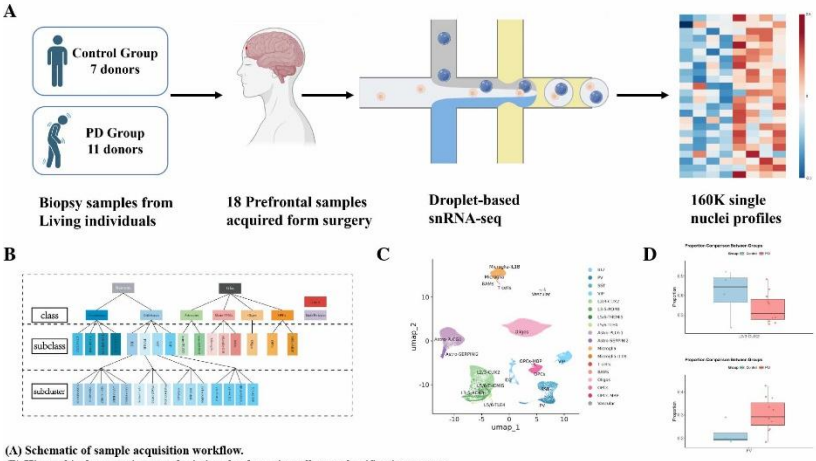
This first atlas of the living PD prefrontal cortex provides a foundation for understanding cell-type-specific vulnerability in early-to-mid-stage disease. In contrast to postmortem studies, we detected no significant glial activation, underscoring the advantage of surgical biopsies for capturing active disease states. These findings nominate transcription factor dysregulation and SEMA3/ANGPT signaling disruption as targets for cell-type-directed therapeutic intervention and provide a molecular framework for investigating clinical subtypes such as freezing of gait.

Single-nucleus transcriptomics of human prefrontal cortex reveals selective neuronal vulnerability

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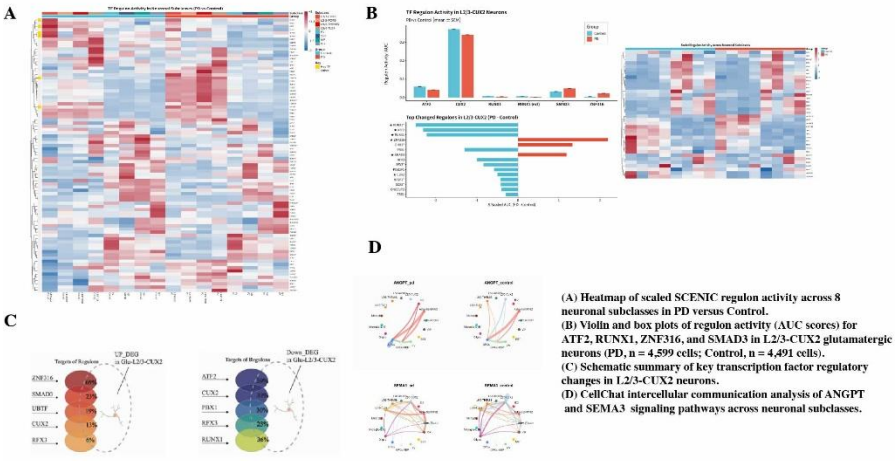
Abstract

Parkinson's disease (PD) is a prevalent neurodegenerative disorder, yet cell-type-specific molecular pathology in the living human prefrontal cortex (PFC) remains poorly characterized. We performed single-nucleus RNA sequencing on fresh surgical biopsies of dorsolateral PFC from 11 sporadic PD patients (4F/7M; mean age 66.4) undergoing deep brain stimulation and 7 normal pressure hydrocephalus controls (2F/5M; mean age 69.7). After stringent quality control and MNN integration, we profiled 118,208 nuclei across a three-tier annotation hierarchy encompassing 8 major cell types and 16 neuronal and glial subclasses. Oligodendrocytes increased (52% vs 24%) and astrocytes decreased (12% vs 25%) in PD. PV GABAergic interneurons were selectively expanded (30% vs 22%, p=0.029), while L2/3-CUX2 glutamatergic neurons trended toward reduction (41% vs 63%), with 2,127 and 566 differentially expressed genes identified, respectively, converging on synaptic signaling and neuronal projection pathways.



(A) Schematic of sample acquisition workflow.
(B) Hierarchical annotation tree depicting the three-tier cell-type classification system.
(C) Uniform Manifold Approximation and Projection (UMAP) embedding of 118,208 single nuclei colored by subclass annotation.
(D) Box plots comparing proportional distribution of L2/3-CUX2 glutamatergic neurons and PV GABAergic interneurons between PD and Control groups.

SCENIC analysis revealed downregulation of ATF2 and RUNX1 regulons and upregulation of ZNF316 and SMAD3 in PD L2/3-CUX2 neurons. CellChat analysis uncovered substantial perturbation of ANGPT and SEMA3 signaling, with SEMA3-mediated excitatory connectivity from L2/3-CUX2 to other glutamatergic subtypes markedly reduced in PD, suggesting disrupted excitation-inhibition balance.



(A) Heatmap of scaled SCENIC regulon activity across 8 neuronal subclasses in PD versus Control.
(B) Violin and box plots of regulon activity (AUC scores) for ATF2, RUNX1, ZNF316, and SMAD3 in L2/3-CUX2 glutamatergic neurons (PD, n = 4,599 cells; Control, n = 4,491 cells).
(C) Schematic summary of key transcription factor regulatory changes in L2/3-CUX2 neurons.
(D) CellChat intercellular communication analysis of ANGPT and SEMA3 signaling pathways across neuronal subclasses.

This first atlas of the living PD prefrontal cortex provides a foundation for understanding cell-type-specific vulnerability in early-to-mid-stage disease. In contrast to postmortem studies, we detected no significant glial activation, underscoring the advantage of surgical biopsies for capturing active disease states. These findings nominate transcription factor dysregulation and SEMA3/ANGPT signaling disruption as targets for cell-type-directed therapeutic intervention and provide a molecular framework for investigating clinical subtypes such as freezing of gait.

Disclosures: Y. Fan: None. **Z. Baorong:** None. **M. Shi:** None. **J. Pu:** None.

Poster

PSTR305: Parkinson's Disease: Cellular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR305.30/W3

Topic: C.03. Parkinson's Disease

Support: R01NS133187

Title: The FBXW7/PGC-1α pathway as a potential therapeutic target for Parkinson's disease.

Authors: *S. TUITHUNG[1,4], S. ELEUTERI[2,4], W. WEI[3,4], D. K. SIMON[2,4];
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Abstract: Objective: To investigate how interplay between the chaperone-mediated autophagy (CMA) and ubiquitination pathways contribute to the regulation of FBXW7 and PGC-1α levels.**Background:** PGC-1α plays a central role in regulating mitochondrial biogenesis and antioxidant defenses. Although enhancing PGC-1α expression in transgenic mice shows potential neuroprotective effects, excessively elevated PGC-1α levels using viral vector-based strategies have been found to impair dopaminergic (DA) neuron survival. Therefore, understanding the endogenous mechanisms regulating PGC-1α may allow more physiological targeting of PGC-1α to achieve therapeutic potential in Parkinson's disease. FBXW7 ubiquitinates PGC-1α, promoting its degradation by the ubiquitin proteasome system (UPS). We hypothesize that FBXW7 is degraded by CMA, thereby reducing UPS mediated degradation of PGC-1α to impact Parkinson disease pathogenesis.**Methodology:** *FBXW7* knockout HCT116 cells were utilized for these experiments. To determine if FBXW7 is a direct substrate of CMA, cells were transiently transfected with mutant FBXW7 constructs in which one or both CMA motifs (KDLLQ and/or QRDFI) were deleted.**Results:** FBXW7 protein levels were absent in HCT116 *FBXW7* knockout cells compared with wild-type HCT116 cells. In contrast, cells expressing single CMA motif deletion mutants showed increased accumulation of FBXW7 protein compared to cells expressing wild-type FBXW7. Notably, FBXW7 expression was further elevated in cells expressing the double-deletion mutant compared with the single-deletion mutants. Importantly, single CMA motif deletion mutants exhibited reduced PGC-1α levels relative to HCT116 *FBXW7* knockout cells. However, cells expressing the double-deletion mutant unexpectedly displayed increased PGC-1α expression compared with the single mutants. We hypothesize that mutations in the CMA motifs may reduce the E3 ligase activity of FBXW7. To further examine this possibility, co-immunoprecipitation assays were performed. FBXW7 pull-down with HSC70 (a key CMA protein) was detected in wild-type cells as well as in cells expressing the single CMA motif deletion mutants, but not in HCT116 *FBXW7* knockout cells.**Conclusion:** These findings indicate that FBXW7 is a downstream target of CMA, supporting our prior work revealing a novel mechanism for regulating PGC-1α, whereby CMA promotes the degradation of FBXW7, thereby reducing UPS-mediated degradation of PGC-1α. Further studies are needed to test our hypothesis that mutating the CMA motifs impairs the E3 ligase activity of FBXW7.

Disclosures: S. Tuithung: None. **S. Eleuteri:** None. **W. Wei:** None. **D.K. Simon:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.01/W4

Topic:

Support: NINDS UH3NS128150
Michael J. Fox Foundation (9605)
NINDS R21 NS096398
Robert and Ruth Halperin Foundation
John E. Cahill Family Foundation

Title: Assessing inter-finger coordination breakdown as a motor biomarker in Parkinson's disease using a quantitative digitography task

Authors: *K. CHIMNI[1], K. B. WILKINS[2], H. BRONTE-STEWART[3], K. W. DALEY[4]; [1]stanford, Palo Alto, CA; [2]Neurol., [3]Neurol. and Neurolog. Sci., Stanford Univ., Palo Alto, CA; [4]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Successful alternating index and middle finger tapping requires neural and biomechanical coupling. Parkinson's disease (PD) disrupts basal ganglia-mediated motor control, impairing not just single-finger kinematics but potentially the coordination between adjacent fingers during alternating tasks. Quantitative Digitography (QDG) measures the kinematics of a 30-second task of repetitive alternating presses and releases of the index and middle fingers on adjacent tension-engineered levers. Metrics of frequency, amplitude, rhythm, and speed have been validated against the MDS-UPDRS III and upper and lower extremity subscores. Whether PD selectively disrupts inter-finger coordination and whether this breakdown serves as a motor biomarker, has not been examined.Data were collected from 39 individuals with PD (off medication) and 29 healthy controls (HC) who performed the QDG task with both hands. Eight metrics were extracted per finger. Inter-finger coordination was quantified as the absolute difference in each metric between the index and middle fingers . A signed difference analysis (index minus middle) was used to determine whether any breakdown in coordination was driven by one finger being consistently worse or reflected a global loss of coordination. Disease duration was additionally examined as a predictor of dissociation within the PD group. Linear mixed-effects models were used to compare groups, with Bonferroni correction applied across all 8 metrics.PD showed significantly greater impairment in inter-finger coordination compared to HC across the majority of metrics ($p = 0.0000017$ - 0.014). Release Slope, a metric correlated with rigidity, showed less variance between the index and middle fingers in PD compared to HC, reflecting the systemic nature of rigidity that couples both fingers toward the same slow release of the lever. Signed analysis did not differentiate either finger as the consistently worse performer in the alternating task suggesting a distributed network failure to coordinate the

adjacent fingers in the task. Disease duration did not predict dissociation after correction.Inter-finger coordination breakdown is a robust, multi-dimensional motor signature of PD measurable in 30 seconds, revealing a dimension of motor dysfunction that single-finger metrics and standard clinical assessments do not capture.

Disclosures: K. Chimni: None. **K.B. Wilkins:** None. **H. Bronte-Stewart:** None. **K.W. Daley:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.02/W5

Topic: C.03. Parkinson's Disease

Title: Evidence for Circadian Modulation of Gait Dysfunction in Parkinson's Disease

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Abstract: Gait impairment is among the most disabling motor manifestations of Parkinson's disease (PD) and often progresses despite optimal dopaminergic therapy. While levodopa improves many cardinal motor symptoms, temporal gait parameters such as stride duration and variability remain relatively resistant to treatment. Timed exposure to bright light (TEBL), a non-pharmacological intervention used to regulate circadian rhythms and melatonin secretion, has been associated with improvements in some motor symptoms in PD. However, previous studies have relied primarily on clinical rating scales rather than objective biomechanical measures of gait. We hypothesized that TEBL would improve gait performance and neuromuscular control in medicated individuals with PD. In a randomized, double-blind, placebo-controlled crossover study, 15 individuals with PD were enrolled, and 13 completed both intervention arms. Participants received either two weeks of TEBL with a wearable blue-green light device (Re-Timer; peak wavelength 525 nm) or placebo light exposure with a modified light device (Re-Timer) featuring dim red LEDs (70 lux), in randomized order, separated by a two-month washout period. Gait assessments were performed before and after each intervention. Participants walked at three different speeds while spatiotemporal gait parameters were recorded using motion capture cameras and an instrumented walkway. Outcome measures included step length, stride length, cadence, stride duration, percent stance and swing time, and lower-extremity muscle activity measured using surface electromyography (EMG). Our results showed that TEBL significantly improved gait performance, resulting in increased step length, increased stride length, increased cadence, and reduced stride duration ($p < 0.05$). Notably, stride duration, a gait parameter often resistant to levodopa treatment, improved following TEBL. TEBL was also associated with a reduction in Tibialis Anterior (TA) EMG bursts during walking. In

contrast, placebo light exposure produced no significant changes in gait or EMG measures ($p > 0.05$). These findings indicate that TEBL improves locomotor function in PD, including gait parameters that are typically resistant to pharmacological treatment. The absence of changes following placebo exposure suggests a specific effect of TEBL on gait control. The observed improvements are consistent with modulation of circadian-dependent neural circuits involved in motor control and provide further support for circadian-based interventions as an adjunctive therapeutic approach for addressing gait dysfunction in PD.

Disclosures: S. Dehghani: None. **E. Hemmati:** None. **L. Alibiglou:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

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Program #/Poster #: PSTR306.03/W6

Topic: C.03. Parkinson's Disease

Support: National Institutes of Health R01NS129115- 02
The Edward and Barbara Bell Family Endowed Chair

Title: Validation of Comprehensive Augmented Reality Testing Platform for Quantifying Functional Mobility Performance in Parkinson's Disease

Authors: *M. MILLER KOOP[1], A. BAZYK[3], C. WALTZ[4], R. KAYA[1], A. ROSENFELDT[3], L. SCELINA[1], J. L. ALBERTS[2];
[2]Biomed. Engin., [1]Cleveland Clin., Cleveland, OH; [4]Biomed. Engin., [3]Cleveland Clin. Fndn., Cleveland, OH

Abstract: Eighty percent of patients with advanced Parkinson's Disease (PD) will fall every year. Despite the prevalence and clinical impact, postural and gait impairments (Postural Instability and Gait Dysfunction [PIGD]) that lead to falls remain difficult to predict and observe in routine clinical evaluations, limiting opportunities for early intervention and prevention. The Timed Up and Go (TUG) test requires participants to sit, stand, turn, and walk in a straight line and is a widely used clinical assessment of functional mobility and fall risk in older adults and in PD. However, the single outcome of total completion time is simplistic and may not detect impairments during this highly complex task that contribute to increased fall risk. The Comprehensive Augmented Reality Testing (CART) platform was designed to provide quantitative measures of postural and gait performance during each subtask of the TUG. Eighty-six participants with PD and 35 age-matched healthy controls (HC) completed the TUG task while wearing an augmented reality (AR) headset (HoloLens 2). Embedded IMU data from the CART headset and 3D motion capture data (MoCap; Vicon Motion Systems) were utilized to construct the following performance metrics to evaluate the criterion and known-groups validity of the CART metrics: Total Time, Sit-to-Stand Time, Gait Ascend and Descend Times, Stand-to-Sit Time, Turn Mean Velocity, and Turn Peak Velocity. Linear mixed models were used to

determine if each of the CART metrics was statistically equivalent to the MoCap values (<5% difference) and could discriminate between HC and PD cohorts at an alpha level of 0.05. All seven CART outcome measures demonstrated statistical equivalence with the gold standard MoCap system. In addition, five of the seven CART performance metrics demonstrated significant differences between the PD and HC cohorts. Specifically, the PD cohort required more time (~1.5 s longer, $p<0.05$) to complete the task compared to the HC cohort, likely due to slower postural transitions (~20%, $p<0.05$) and reduced turning velocities (~12%, $p<0.05$). Together, these results demonstrate that the CART platform provides valid measures of PIGD that are sensitive to PD-related impairments. Moreover, these findings support the future use of the AR capabilities of the CART platform to assess functional mobility during more ecologically valid, real-world tasks in clinical settings, which may improve the identification and treatment of PIGD and help prevent falls in individuals with PD.

Disclosures: M. Miller Koop: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Strolll Limited. **A. Bazyk:** None. **C. Waltz:** None. **R. Kaya:** None. **A. Rosenfeldt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stroll Limited. **L. Scelina:** None. **J.L. Alberts:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stroll Limited.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.04/W7

Topic: C.03. Parkinson’s Disease

Title: Learning-Related Thalamomotor Plasticity in Parkinson’s Disease Revealed by DTI and Resting-State fMRI

Authors: *A. AMEDI[1], E. SASSON[2], T. TAMIR[3], M. CATALOGNA[1];
[1]Reichman Univ., Herzliya, Israel; [2]WiseImage, Utrecht, Netherlands; [3]Remepy Hlth. Ltd., Tel Aviv, Israel

Abstract: Parkinson’s disease (PD) is associated with progressive disruption of thalamocortical motor networks, yet the neural mechanisms underlying short-term learning-induced plasticity and their relationship to clinical improvement remain incompletely understood. Diffusion tensor imaging (DTI) is sensitive to rapid microstructural adaptations associated with learning and may provide a biomarker of treatment-induced plasticity. We investigated whether a short digital intervention could induce structural and functional changes in motor networks and whether these changes were associated with motor outcomes in levodopa-treated PD. In a prospective, randomized, double-blind, placebo-controlled study, 39 patients with PD underwent clinical assessments and 32 of them underwent MRI scans, including DTI and resting-state functional

MRI (rs-fMRI), pre- and post-treatment. Participants were randomized to DopApp, a digital treatment combining multisensory spatial navigation training with motor and psychological modules, or a placebo app. Clinical outcome included the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Neuroimaging analyses evaluated DTI metrics, graph-theoretical measures, and functional connectivity. Compared with placebo, DopApp significantly improved total MDS-UPDRS scores (between-group difference 7.75 points, p=0.0005), driven by gains in Parts II and III. DTI revealed increased fractional anisotropy in the right ventrolateral posterior (VLp) thalamus following treatment. Rs-fMRI demonstrated strengthened functional connectivity between the VLp and precentral gyrus (PreCG), while graph-theoretical analyses showed increased local efficiency within the PreCG and its neighboring motor- basal ganglia network. These neuroimaging changes were associated with motor improvement. Among participants completing the spatial navigation task (n=15), higher spatial learning performance was associated with greater improvement in MDS-UPDRS Part III scores (Spearman r=-0.61, p=0.016) and remained an independent predictor of motor outcome after adjustment for baseline severity (β=-4.40, p=0.036). These findings demonstrate that brief interventions that include spatial learning can induce measurable microstructural and functional plasticity within thalamomotor networks in PD. The convergence of DTI, rs-fMRI connectivity, network analyses, and behavioral learning measures supports neuroimaging biomarkers of learning-related plasticity and highlights the potential of digital treatment to augment dopaminergic treatment through learning-dependent neural mechanisms.

Disclosures: A. Amedi: A. Employment/Salary (full or part-time):; Remepy Health Ltd.. **E. Sasson:** None. **T. Tamir:** A. Employment/Salary (full or part-time):; Remepy Health Ltd. **M. Catalogna:** A. Employment/Salary (full or part-time):; Remepy Health Ltd..

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.05/W8

Topic: C.03. Parkinson's Disease

Support: klef doctoral fellowship 002

Title: Integrated MRI Imaging and Blood-Based Biomarkers for Early Diagnosis and Progression of Parkinson's Disease

Authors: *L. EMANI[1], J. KOSAGISHARAF[2,3];
[1]Biotech., KLEF Deemed to be Univ., Guntur, India; [2]Ctr. for Neurosci., INDICASAT AIP, Panama City, Panama; [3]Biotech., KLEF DEEMED TO BE UNIVERSITY, Vaddeswaram, India

Abstract: Integrated MRI Imaging and Blood-Based Biomarkers for Early Diagnosis and Progression of Parkinson's Disease
Lakshmi Sowmya E[1], Jayanth KS Rao[2,] Pranathi Jalapally[3] , Keshav Raichurkar P[4], Sminu

Izudheen [5] , Sathyanarayana Rao T.S[6] , Jagannatha Rao KS[1]
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Abstract Parkinson's disease (PD) is a rapidly growing neurodegenerative disorder, with global prevalence projected to triple by 2050. Despite advances in understanding its complex etiology and pathology, **early and reliable diagnosis of PD remains a significant clinical challenge**. The present study aims to develop an integrated diagnostic framework by combining **MRI-based neuroimaging and blood-based biomarkers** to distinguish early and progressive stages of PD. We performed detailed MRI analyses to evaluate regional brain atrophy, focusing on the hippocampus, frontal lobe, temporal lobe, thalamus, cerebellum, caudate nucleus, substantia nigra, and midbrain. Our findings revealed **highly significant atrophy ($p < 0.001$)** in the caudate nucleus, thalamus, hippocampus, and substantia nigra in PD patients compared to healthy controls. Moderate reductions were observed in the frontal lobe, temporal lobe, and midbrain regions, although these changes did not reach statistical significance ($p < 0.05$). No significant structural differences were detected in the cerebellum. The blood-based analyses in the same patients demonstrated that **ceruloplasmin and ferritin levels were significantly reduced**, whereas **α-synuclein, 8-hydroxyguanosine (8-OH-G), and total antioxidant activity were elevated** in PD patients. Additionally, trace element profiling indicated decreased levels of copper (Cu) and iron (Fe), alongside increased zinc (Zn) levels, suggesting altered metal homeostasis and oxidative stress involvement in PD pathology. Collectively, our findings highlight the potential of **integrated imaging and circulating biomarker signatures** as a robust, non-invasive approach for the **early diagnosis and staging of Parkinson's disease**. Furthermore, the incorporation of computational analysis for multi-modal data integration enhanced diagnostic accuracy and support improved clinical management strategies.

Disclosures: L. Emani: None. **J. Kosagisharaf:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

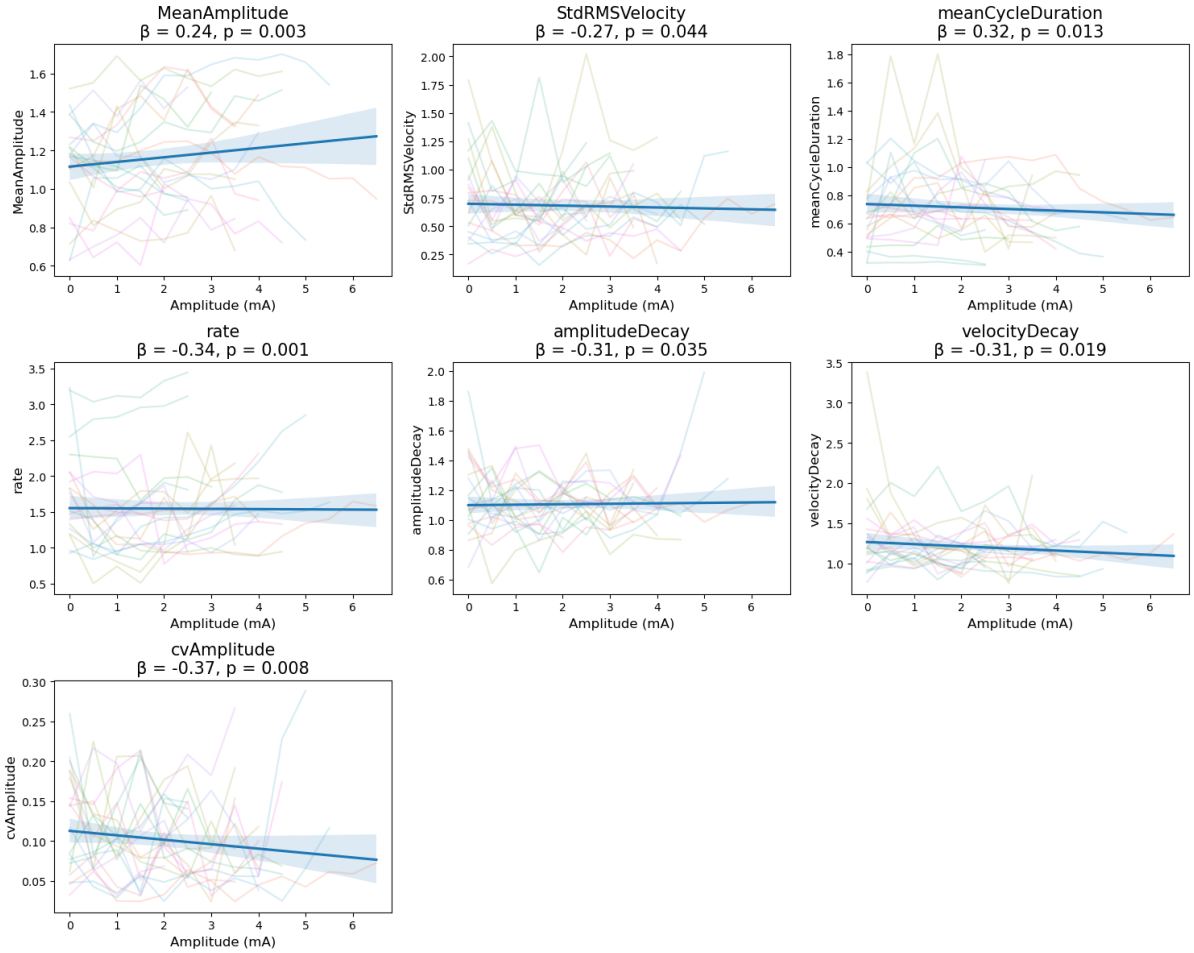
Program #/Poster #: PSTR306.06/W9

Topic: C.03. Parkinson's Disease

Title: Digital Kinematic Measures of Finger Tapping Detect Dose-Dependent Effects of Deep Brain Stimulation in Parkinson's Disease

Authors: *G. ACEVEDO[1], D. VUDDANDAM[1], A. MADAMANGALAM[1], G. KENWORTHY[1], J. CAGLE[2], C. DE HEMPTINNE[1], J. WONG[1];
[2]J. Crayton Pruitt Family Dept. of Biomed. Engin., [1]Univ. of Florida, Gainesville, FL

Abstract: DBS improves bradykinesia in Parkinson's disease (PD), but objective quantification of motor changes during stimulation adjustment remains limited. Video-based kinematic analysis offers a scalable and objective approach to quantify digital movement measures associated with bradykinesia. The aim of this study was to evaluate whether video-based digital kinematic measures can quantify dose-dependent changes in finger tapping performance during DBS in PD. Eleven PD patients with DBS (20 hands) performed repetitive finger tapping while stimulation amplitude was increased from 0 mA to the side-effect threshold in 0.5 mA increments. After each amplitude adjustment, participants rested for 30 seconds before performing 10 repetitions of index-thumb tapping with maximal movement amplitude. Videos were analyzed using VisionMD to extract digital kinematic measures previously associated with movement impairment in PD. Linear mixed-effects models with random intercepts and slopes for each hand tested the relationship between stimulation amplitude and each digital measure, including both linear and quadratic amplitude terms. Several digital measures demonstrated significant modulation with increasing DBS amplitude. Linear dose-response relationships were observed for movement amplitude (increase), amplitude variability (decrease), RMS velocity variability (decrease), amplitude decay (decrease), velocity decay (decrease), cycle duration (increase), and rate (decrease). Additional measures, primarily reflecting movement speed and variability, showed nonlinear modulation across stimulation levels. Overall, DBS-responsive digital measures corresponded to established domains of bradykinesia, including movement amplitude, speed, rhythm, and sequence effect. Video-derived digital kinematic measures detected dose-dependent motor changes during DBS modulation and captured multiple dimensions of bradykinesia, supporting the use of video-based movement analysis for quantifying DBS-related motor effects.



Disclosures: G. Acevedo: None. **D. Vuddandam:** None. **A. Madamangalam:** None. **G. Kenworthy:** None. **J. Cagle:** None. **C. de Hemptinne:** None. **J. Wong:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.07/W10

Topic: C.03. Parkinson’s Disease

Support: Queen Elizabeth II Graduate Scholarship in Science & Technology
Canadian Institute of Health Research (CIHR) (PJT-173540)
Krembil-Rossy Chair Program

Title: Development of a Neural Network Pipeline to Assess MRI for Detection of Parkinson's Disease

Authors: *A.-G. DENNIS[1,2], C. CAMASTRA[3], R. CHEN[1,2], P. GERRETSEN[1,3], A. P. STRAFELLA[1,2,3];
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Abstract: Up to 62% of individuals with Parkinson's disease (PD) experience cognitive impairment, and around 30% of patients with PD develop dementia. An early diagnosis could reduce caregiver burden and increase treatment rates. However, there is currently no standard biomarker for PD that can be used in clinical practice. Numerous studies have found that imaging is instrumental in the tracking of PD and that machine learning can assist with detection, although many machine learning models cannot be validated past the research stage. Structural MRI is useful, as it can be used to assess changes in anatomy. It is possible that MRI can be used with machine learning to distinguish stages of PD. Therefore, this research aims to develop a validated MRI-based machine learning model to identify PD. All data was sourced from the Parkinson's Progression Markers Initiative and imaging was preprocessed in Matlab using the SPM12 and CAT12 toolboxes. The sample included 537 patients, with 179 healthy controls, 179 patients determined to be at-risk of developing PD, and 179 patients diagnosed with PD. To assess the MRI, I am using a convolutional neural network structure, which can analyze images without losing anatomical connections. Models are constructed using the Python programming language. Computations were performed on the Trillium supercomputer at the SciNet HPC Consortium. Three convolutional layers were used to assess and extract features from the initial MRI imaging for each patient. Four linear artificial neural network functions were then applied to reduce the size of the extracted features and output a classification. 70% of the sample was used to train the model, 15% of the sample was used to refine and validate the model's parameters, and the final 15% was used to evaluate the model's performance. The model functions with accuracy up to 67% when aiming to distinguish patients diagnosed with PD from healthy patients, and accuracy was up to 72% when distinguishing at-risk patients from healthy patients. The ability of the model to correctly classify patients with PD or at-risk patients was higher, between 74% and 82%. The model was less capable when correctly classifying healthy patients, with numerous false positives. Continuing work will focus on fine-tuning the model and further improving performance. Through machine learning, I will create a model that can be adapted into clinical settings for diagnosis and assessment of PD. If my model can be implemented into clinical practice, more patients with PD may receive treatment to delay progression and reduce the effect of symptoms on the patient's wellbeing.

Disclosures: A. Dennis: None. **C. Camastra:** None. **R. Chen:** None. **P. Gerretsen:** None. **A.P. Strafella:** 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.; PJT-173540.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.08/W11

Topic: C.03. Parkinson's Disease

Support: LB692 Nebrask Biomedical Research Development Fund
Dr. George F. Haddix President's Faculty Research Fund (Creighton)
Health Science Strategic Investment Fund 201038-823260

Title: Biomarker discovery using blood exosomes for Parkinson's disease.

Authors: *B. KANG[1], J. LOUIE[1], L. COPE[1], H. KIM[1], H. KIM[1], N. SANDE[1], J. BAHN[1], Y. CHAE[1], M. S. BURNETT[2], J.-Y. HWANG[1];
[1]Pharmacol. and Neurosci., Creighton Univ. Sch. of Med., Omaha, NE; [2]Dept. of Neurol., Creighton Univ. Sch. of Med., OMAHA, NE

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. PD is caused by the progressive loss of nigrostriatal dopaminergic neurons and is characterized by increases in cytoplasmic inclusions of alpha-synuclein. Timely diagnosis of PD is critical to providing the proper treatment and care planning, however, current diagnostic laboratory tests for PD are limited. Therefore, identification of reliable biomarkers is clinically imperative. Exosomes are nanovesicles found throughout the body that carry various proteins, mRNAs, and microRNAs. Central nervous system (CNS)-derived exosomes can cross the blood-brain barrier and have been suggested as potential biomarkers in some pilot studies. Thus, research related to a further validation and a large independent cohort study is needed for relevancy and accuracy. To examine the possibility of using CNS-derived exosomes as biomarkers and identify novel candidates, we isolated CNS-derived exosomes from the peripheral blood of PD patients and age-matched healthy controls. The results from Western blot analysis using the antibody against L1CAM, a marker for CNS exosomes, showed that CNS-derived exosomes are successfully isolated from blood. Additionally, we validated the presence and size of the isolated CNS-derived exosomes using transmission electron microscopy (TEM). We then examined whether PD-related pathogenic proteins, including Parkin, PINK1, DJ-1, GBA, and phosphorylated α-synuclein are altered in these exosomes. Our findings indicate that a subset of these proteins significantly differ between PD patients and healthy controls, suggesting their potential use as diagnostic biomarkers. To further identify novel candidates, we are currently conducting a proteomic analysis of CNS-derived exosomes. We anticipate this analysis will uncover novel protein biomarkers for the diagnosis of PD.

Disclosures: B. Kang: None. **J. Louie:** None. **L. Cope:** None. **H. Kim:** None. **H. Kim:** None. **N. Sande:** None. **J. Bahn:** None. **Y. Chae:** None. **M.S. Burnett:** None. **J. Hwang:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.09/W12

Topic: C.03. Parkinson's Disease

Support: MJFF Grant 2023-023629

Title: Serum Lysosomal Proteins as Candidate Biomarkers in Parkinsonian Disorders

Authors: *B. DEHAY[1], D. BENDETOWICZ[1,2], E. BEZARD[1], V. PLANCHE[1,3], W. MEISSNER[1,2];
[1]Inst. of Neurodegenerative Dis., Bordeaux Cedex, France; [2]Service de Neurologie des Maladies Neurodégénératives, IMNc, CRMR AMS, NS-Park/FCRIN Network, [3], Pôle de Neurosciences Cliniques, Ctr. Mémoire de Ressources et de Recherche, CHU de Bordeaux, Bordeaux, France

Abstract: The development of reliable biomarkers to aid diagnosis and provide objective measures of disease progression in Parkinson's disease (PD) remains an unmet clinical need. Developing biomarkers is also essential to provide objective endpoints for future disease-modification trials. Given the role of lysosomal dysfunction in PD pathophysiology, we first assessed the lysosomal cation-transporting ATPase, ATP13A2. Loss-of-function mutations in *ATP13A2* are causally linked to a form of early-onset atypical PD, and the phenotypic spectrum associated with genetic variants in *ATP13A2* now becomes more and more complex. Second, we measured one of the interesting lysosomal cathepsin enzymes, cathepsin K (CTSK), which shows a strong affinity for alpha-synuclein. Here, we investigated the sensitivity and specificity of this duet of potential biomarkers by ELISA in a longitudinal, well-characterised, and unique cohort of non-human primates (NHPs) injected with patient-derived tau or alpha-synuclein aggregates and in an existing cohort of subjects with PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and healthy controls. Specific ELISA assays were used to determine relative protein expression levels in serum samples from the NHP cohort and from subjects with MSA (n=64), PD (n=35), and PSP (n=25), and healthy controls (HC) (n=22). We also evaluated longitudinally-collected serum samples (Control n=7, PSP n=16, MSA n=29). In NHPs, statistical analysis did not identify significant differences across post-injection time points within the experimental groups and the diseases they model. However, in humans, statistical models identified disease-specific effects for the two biomarker candidates in both serum and longitudinal samples. For CTSK, we observed a significant decrease in the PD and PSP groups compared to the MSA and HC groups, whereas for ATP13A2, we observed a significant increase in the PD group compared to the HC group. Further analysis is necessary to address the association between serum ATP13A2 and CTSK levels with clinical features associated with each neurodegenerative disease. Overall, this study might represent an advance in our ability to design a specific lysosomal biomarker for PD. This ability will lead to a much-improved understanding of the mechanisms of lysosomal contribution and also of its role in PD etiology.

Disclosures: B. Dehay: None. **D. Bendetowicz:** None. **E. Bezard:** None. **V. Planche:** Other; During the past three years, V.P. was a local unpaid investigator or sub-investigator for clinical trials granted by Novo Nordisk, Janssen, Alector, BMS and Roche. **W. Meissner:** Other; Consultancy fees from Lundbeck, Koneksa, Ferrer, Takeda, BioArctic, Teva, and Abli. Lecturing fees from Lundbeck.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.10/W13

Topic: C.03. Parkinson's Disease

Title: Auditory & Vestibular Markers for Understanding Cognition in Parkinson's Disease

Authors: *C. ALVAREZ[1], A. DANESH[2];
[1]Florida Atlantic Univ., West Palm Beach, FL; [2]Florida Atlantic Univ., Boca Raton, FL

Abstract: Parkinson's disease (PD) has become the leading neurodegenerative disorder in terms of incidence, characterized by a highly variable symptom profile. Despite the progress in understanding and treating PD, fall risk remains high, and the overall quality of life remains low. Among the less understood non-motor symptoms is cognitive decline, which is often reported subjectively by individuals with PD without formal clinical diagnosis. Growing evidence indicates that inner-ear sensory systems, integral to hearing and balance, may play a crucial role in the clinical presentation of symptoms in PD. While vestibular dysfunction (VD) has been linked to motor symptoms, its contribution to cognitive changes is less well-defined. Additionally, hearing loss (HL), recognized as the most modifiable risk factor for dementia, has not been thoroughly examined in conjunction with VD within this population. This study investigates the interactions between hearing status, vestibular function, and cognition in PD, utilizing a comprehensive assessment battery that includes self-report questionnaires, pure-tone audiometry, cognitive tests, balance assessments, and oculomotor evaluations. Participants were grouped based on disease duration and hearing status. Preliminary findings indicate that individuals with early-stage PD and mild HL exhibit reduced vestibular performance and impaired cognitive function, particularly in visuospatial domains, compared to peers with normal hearing. Notably, these performance patterns resemble those observed in later stages of PD. Although initial data is limited (n = 3 per group), significant differences emerged in balance measures, visuospatial cognition, and vertical saccade metrics. Continued recruitment and data collection will further elucidate these relationships, with the ultimate goal of identifying sensitive sensory-based biomarkers to inform future diagnostic and rehabilitative strategies.

Disclosures: C. Alvarez: None. **A. Danesh:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.11/W14

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Foundation (MJFF-025372)

Title: Distinct immune profiles are associated with Parkinson's disease susceptibility and disease outcomes in a large, population-based study

Authors: *L. BLACKMER-RAYNOLDS[1], J. M. BRONSTEIN[1], B. RITZ[2,1], K. PAUL[1]; [1]Neurol., UCLA Geffen Sch. of Med., Los Angeles, CA; [2]Epidemiology, UCLA, Los Angeles, CA

Abstract: Parkinson's disease (PD) is associated with alterations in both innate and adaptive immune activation that are thought to modulate disease susceptibility and progression. Several studies have identified changes in specific cytokines and chemokines in PD, however, many of these studies represent small patient populations or lack longitudinal clinical follow-up, making it difficult to identify consistent immune changes associated with PD outcomes. Large, longitudinal, population-based studies are therefore needed to define immune signatures associated with PD progression. The present study analyzed plasma and serum samples from the Parkinson's Environment and Genes study, a population-based cohort of PD patients and controls from Central California with longitudinal clinical evaluations of motor and non-motor symptoms across 2-4 visits. A panel of 38 cytokines, chemokines, and growth factors was used to evaluate immune activation in 1,572 samples from 1,141 participants (777 PD and 364 controls), including 273 individuals with both baseline and follow-up immunoassay data. Linear regression and mixed effects models were performed to evaluate the relationship between each individual immune marker and PD status as well as motor and non-motor symptoms at both baseline and follow up. From this, several immune markers were identified as particularly important for PD outcomes. For example, increases in epidermal growth factor (EGF) and macrophage colony stimulating factor (M-CSF also known as CSF1) were the most strongly associated with PD status within our study population. Further, clustering of both immune markers and PD patients into immunological subtypes was performed to better understand the relationships between different immune markers and establish a more comprehensive picture of the association between overall systemic immune environments and PD outcomes. Results identify distinct protective and detrimental immune phenotypes that are far more predictive of PD outcomes than any one immune marker. For example, an overall reduction in immune makers (including both classically pro- and anti-inflammatory markers) was associated with a decreased odds of having PD. In contrast, PD was associated with an immune profile characterized by increased levels of a range of immune markers including platelet derived growth factors and interferon gamma. Together, these results emphasize that PD progression is influenced by the broader immune context rather than isolated inflammatory signals, supporting a shift from single-biomarker approaches toward systems-level characterization and therapeutic targeting of immune activation in PD.

Disclosures: L. Blackmer-Raynolds: None. **J.M. Bronstein:** None. **K. Paul:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.12/W15

Topic: C.03. Parkinson's Disease

Support: Swiss National Science Foundation [grant n. 188798]
Swiss National Science Foundation [grant n. 221182]
CARIGEST SA (Fondazione Teofilo Rossi di Montelera e di Premuda and a second one wishing to remain anonymous)
Leenaards Foundation
Synapsis Foundation

Title: Sleep-like slow waves during wakefulness are associated with hallucinations and poorer cognition in Parkinson's disease

Authors: *F. BERNASCONI[1], T. ANDRILLON[3], J. FARAH[2], I. ARNULF[4], S. SCHWARTZ[5], J. POTHEEGADOO[1], A. MARTINEZ-HORTA[6], J. PAGONABARRAGA[7], J. KULISEVSKY[8], O. BLANKE[9];
[1]Ecole Polytechnique Federale de Lausanne (EPFL), Geneva, Switzerland; [2]Ecole Polytechnique Federale de Lausanne (EPFL), Pully, Switzerland; [3]Ecole Normale Superieure, Paris, France; [4]Hôpital Pitié-Salpêtrière, Paris, France; [5]Neurosci., Univ. Hosp. of Geneva, Geneva, Switzerland; [6]Ctr. for Neurosci., UC Davis, Davis, CA; [7]Sant Pau Hosp., Barcelona, Spain; [8]Univ. Autònoma de Barcelona, Barcelona, Spain; [9]Bâtiment H4, EPFL - SV - CNP - LNCO, Geneve, Switzerland

Abstract: Slow waves during sleep are fundamental for neural homeostasis, metabolic regulation, and waste clearance, and are known to be altered in neurodegenerative diseases. Sleep-like slow waves (SLSW) have been observed in awake, healthy individuals, where they are linked to fluctuations in vigilance and mind-wandering. Whether SLSW are altered in Parkinson's disease (PD), and whether such alterations contribute to psychiatric or cognitive complications, remains unknown. In a cohort of 84 non-demented PD patients and 30 healthy older adults, we found that SLSW occurred more frequently in PD. Hallucinatory traits in PD were associated with higher SLSW amplitude, especially over fronto-central regions, and the extent of SLSW alterations was associated with the severity of hallucinatory burden. Moreover, more prominent SLSW were associated with poorer cognitive functions. We conclude that, while slow waves during sleep have positive physiological functions, exacerbated diurnal SLSW may reflect responses related to PD neuropathology, at the cost of hallucinations and reduced cognitive function.

Disclosures: F. Bernasconi: None. **T. Andrillon:** None. **J. Farah:** None. **I. Arnulf:** None. **S. Schwartz:** None. **J. Potheegadoo:** None. **A. Martinez-Horta:** None. **J. Pagonabarraga:** None. **J. Kulisevsky:** None. **O. Blanke:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.13/W16

Topic: C.03. Parkinson's Disease

Title: Structural and Free-Water MRI Markers of Nucleus Basalis of Meynert Degeneration Across the Parkinson's Disease Cognitive Spectrum

Authors: A. NEGIDA[1], M. BARRETT[2], R. HALLAK[2], A. BELNAVIS[3], B. BERMAN[2], ***E. OFORI**[4];
[1]Virginia Commonwealth Univ., Richmond, VA; [2]Virginia Commonwealh Univ., Richmond, VA; [3]Arizona State Univ., Tempe, AZ; [4]Arizona State Univ., PHOENIX, AZ

Abstract: Cognitive impairment in Parkinson's disease (PD) is closely linked to degeneration of the cholinergic basal forebrain, yet structural atrophy and diffusion-derived free water have rarely been integrated across the PD cognitive spectrum. We examined whether multimodal MRI measures of cholinergic nucleus 4 (Ch4; nucleus basalis of Meynert) and cholinergic nuclei 1-3 (Ch1-3; medial septal/diagonal band complex) distinguish cognitive stages and relate to cognitive performance. Ninety-two participants underwent 3T MRI and neuropsychological testing: 14 healthy controls, 35 PD with normal cognition (PD-NC), 33 PD with mild cognitive impairment (PD-MCI), and 10 PD with dementia (PDD). T1-weighted MRI was used to estimate total intracranial volume-normalized gray matter density (GMD), and diffusion MRI was used to estimate free-water (FW) fraction within probabilistic basal forebrain regions of interest. Group differences were tested using Kruskal-Wallis and Bonferroni-corrected Mann-Whitney U tests; cognition-imaging associations in PD were tested using Spearman correlations and covariate-adjusted multivariable regression. Ch4 GMD differed across groups ($p<0.001$), with lower values in PDD than PD-MCI ($p=0.007$), PD-NC ($p<0.001$), and controls ($p<0.001$). Ch4 FW and Ch1-3 FW were elevated in PDD versus all other groups (all $p<0.01$). Among PD participants (n=78), Montreal Cognitive Assessment (MoCA) score correlated positively with Ch4 GMD ($\rho=+0.49$) and Ch1-3 GMD ($\rho=+0.42$), and negatively with Ch4 FW ($\rho=-0.51$) and Ch1-3 FW ($\rho=-0.40$; all $p<0.001$). In a full four-metric model adjusted for age, sex, and education, Ch4 GMD ($\beta=+2.04$, $p<0.001$) and Ch4 FW ($\beta=-1.46$, $p=0.005$) were the only independent basal forebrain predictors of MoCA. Exploratory receiver-operating-characteristic analyses showed that combined Ch4 GMD+FW discriminated PDD from non-demented PD with high apparent accuracy (AUC=0.934; optimism-corrected AUC=0.925) and discriminated cognitively impaired PD from PD-NC with moderate accuracy (AUC=0.788; optimism-corrected AUC=0.773). These findings suggest that structural and free-water MRI capture complementary aspects of Ch4 degeneration relevant to cognitive impairment in PD. Longitudinal and externally validated studies are needed to determine whether Ch4 FW precedes atrophy and improves prediction of conversion from PD-MCI to PDD.

Disclosures: A. Negida: None. **M. Barrett:** None. **R. Hallak:** None. **A. Belnavis:** None. **B. Berman:** None. **E. Ofori:** None.

Poster

PSTR306: Parkinson's Disease: Biomarkers

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR306.14/W17

Topic: I.04. Executive Functions

Support: NIH Grant R01NS129115- 02
NIH Grant UM1TR004528

Title: Understanding the cognitive and motor contributions of iADL function in Parkinson's Disease

Authors: *R. KAYA[1,2], A. BAZYK[2], E. ZIMMERMAN[2], C. WALTZ[3], A. ROSENFELDT[4], M. MILLER KOOP[3], J. L. ALBERTS[3];
[1]Cleveland Clin., Cleveland, OH; [2]Neurolog. Inst., [3]Biomed. Engin., [4]Cleveland Clin. Fndn., Cleveland, OH

Abstract: Cognitive impairment occurs in approximately 25% of people with Parkinsons Disease (PD). Instrumental activities of daily living (iADL) require intact motor and cognitive functions. Current iADL assessments are limited in objectively evaluating iADL independence and lack the fidelity to disentangle motor from cognitive impairments. Mixed reality headset applications can simulate real-world iADL challenges while measuring motor and cognitive function. The Microsoft HoloLens 2 (HL2) headset can capture eye gaze fixations that are related to cognitive decline in PD. The aim of this project was to create an iADL assessment in the HL2 to understand the motor and cognitive contributions to iADL function in healthy older adults and people with PD. An iADL assessment for the HL2 was developed with Unity. Participants donned the HL2 and were instructed through the headset to select four items from a digital vending machine. A distractor item and extraneous information to discriminate from task relevant information were contained in the instructions. Instructions were able to be reviewed as frequently as deemed necessary during the trial. The trial terminated when the correct items were selected, or at 300-seconds. Position data of the hand was sampled at 60 Hz. Eye gaze was the resultant gaze vector of the right and left eyes sampled at 30 Hz. The PD group was assessed OFF-medication. Non-normally distributed ordinal data were analyzed with a Mann Whitney U test and reported as median (IQR). Binary data were assessed with Chi-square tests and normally distributed proportion data with Welch's t-test. Data were reported as percentages. Eighty-nine PD and 36 HC participated, 76% PDs and 78% HCs had gaze data. Task accuracy was greater in HCs (100% vs. 74%, $p < 0.01$) while having a shorter time to completion (123.7 (73.9-168.8) vs 156.4 (108.4-294.4) seconds, $p<0.01$). The number of submission attempts (HC: 2 (1-4), PD: 2 (1-3), $p=0.52$) and instructions reviewed (HC: 3 (1-4), PD: 3 (2-5), $p=0.51$) were similar. Total buttons pressed were also similar between groups (HC: 14.5 (8-22), PD: 13 (8-20), $p=0.83$). The proportion of a correct item being selected first favored HCs (67% vs 38%, $p<0.01$) while PDs disproportionately reviewed the instructions first (43% vs 17%, $p<0.01$). A greater percentage of the trial was spent in gaze fixation for PD (46% vs 38%, $p<0.001$). The simulated but ecological iADL assessment demonstrates the ability to extract cognitive contributions in the form of prolonged gaze fixations correlating with worse performance outcomes in PD. Additionally, short term memory and complex attention impairments in PD were observed by the inaccuracy of first item selected.

Disclosures: R. Kaya: None. **A. Bazyk:** None. **E. Zimmerman:** None. **C. Waltz:** None. **A. Rosenfeldt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Strolll Limited. **M. Miller Koop:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Strolll Limited. **J.L. Alberts:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Strolll Limited.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.01/W18

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: CPSF-GP 2025M782639

Title: Investigating the pathogenic mechanism of SCA51 using Thap11-polyQ knock-in mouse models

Authors: *E. RUAN[1], S. YANG[2];
[1]Jinan University, Med. Sch. - First Clin. Med. Col., Guangzhou, China; [2]Jinan Univ., Guangzhou, China

Abstract: Objective Spinocerebellar ataxia type 51 (SCA51) is a neurodegenerative disorder caused by CAG repeat expansions in the Thap11 gene, leading to polyglutamine (polyQ) tract elongation in the Thap11 protein. The underlying pathogenic mechanism remains largely unknown. This study aims to elucidate the molecular and cellular pathogenesis of SCA51 by establishing novel mouse models and dissecting the dose-dependent effects of polyQ expansion. **Methods** Thap11-47Q (threshold expansion) and Thap11-100Q (severe expansion) knock-in mouse models were generated using CRISPR/Cas9 technology. For behavioral assessment, motor function was evaluated by rotarod, balance beam, and CatWalk gait analysis. For pathological analysis, Nissl staining, immunohistochemistry, and western blotting were used to assess Purkinje cell loss, mutant protein aggregation, and expression of neuron-related proteins. For mechanistic exploration, co-immunoprecipitation coupled with proteomics mapped the interactome of mutant Thap11; ATAC-seq and CUT&TAG assays were performed to analyze genome-wide chromatin accessibility and protein-DNA binding.**Results** Thap11-100Q mice exhibit earlier disease onset, more severe motor deficits, and more significant Purkinje cell loss relative to Thap11-47Q mice. Mutant Thap11 abnormally recruits transcriptional co-factors, remodels its genomic binding patterns, and triggers gene expression alterations in a CAG repeat length-dependent manner. Purkinje cells are confirmed as the most vulnerable cell type in SCA51 pathogenesis, and conditional expression of mutant Thap11 is sufficient to recapitulate typical ataxia-like phenotypes in mice. **Conclusion** Mutant Thap11 drives neurodegeneration through a polyQ dose-dependent gain-of-function mechanism, providing a theoretical basis and candidate targets for precision stratified therapy of SCA51.

Disclosures: E. Ruan: None. **S. Yang:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.02/W19

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: RO1: 4R37NS027699-37

Title: DEVELOPING REGION-SPECIFIC ATXN1 INTERACTOME TO GAIN INSIGHT INTO SCA1 PATHOGENESIS

Authors: *E. RIVERA[1,2], J. SONN[1,2], E. CHU[1,2], T. GONZALEZ-ROBLES[1,2,3], R. MEYER-SCHUMAN[1,2], H. Y. ZOGHBI[1,2,3];
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Abstract: Spinocerebellar Ataxia Type 1 (SCA1) is a progressive, autosomal dominant neurodegenerative disorder characterized by impaired motor coordination and balance. The disease is caused by an abnormal expansion of a CAG trinucleotide repeat in the Ataxin-1 gene (ATXN1). ATXN1 is widely expressed in the CNS and regulates gene expression through its interaction with the transcriptional repressor Capicua (CIC). Several studies have shown that polyglutamine-expanded ATXN1 (PolyQ-ATXN1) exerts its toxicity through a gain-of-function mechanism. PolyQ-ATXN1 increases genome-wide CIC binding, resulting in the hyper-repression of its target genes. Disruption of the mutant ATXN1-CIC complex restores CIC DNA binding to wild-type levels and rescues the expression of the CIC-regulated genes. However, this benefit is mostly seen in Purkinje cells while minimal in other cerebellar cells and the brainstem, suggesting other factors may play a role in mediating the toxicity of polyQ-ATXN1. To identify additional factors that contribute to SCA1 pathogenesis, we performed an ATXN1 proteomic study in mouse brainstem, hippocampus, striatum and cortex. Given that nuclear localization is required for polyQ-ATXN1 to exert its toxicity, and the persistence of gene expression abnormalities following disruption of the polyQ-ATXN1-CIC toxic complex, we focused on transcription factors that interact with ATXN1 independently of CIC. Our analyses identified the transcription factors RFX1 and ZKSCAN1 as selective ATXN1 interactors in the brainstem. These results are consistent with previous work, in which RFX1 and ZKSCAN1 were identified as ATXN1-interacting proteins in the cerebellum. To investigate the role of RFX1 in SCA1 pathogenesis, we are performing CUT&Tag to define its genome-wide DNA-binding profile and correlate these data with the transcriptional changes in *Sca1*$^{154Q/+}$ mice. We identified a small number of transcription factors in the striatum (HMBOX1 and BCL11b) and cortex (CUX1 and SATB2), that interact with ATXN1 through CIC. Interestingly, no additional transcription factors were identified in the hippocampus, a region in which disruption of the polyQ-ATXN1-CIC interaction fails to rescue pathology, suggesting that mutant ATXN1 toxicity may be

mediated through alternative molecular mechanisms. Collectively, these findings indicate that ATXN1 interacts with distinct transcription factors in a region-specific manner, with some factors (RFX1 and ZKSCAN1) shared across brain regions. Importantly, our findings highlight the complexity of disease pathogenesis with different factors and mechanisms at play in different brain regions.

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Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.03/W20

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: Freedom Together Foundation

Title: Investigating the role of moderate and systemic CHIP overexpression in a Spinocerebellar Ataxia Type 1 mouse model

Authors: *E. GARCIA[1], E. XHAKO[2], X. DENG[1], J. KIM[2], D.-E. C. CHUNG[1], I. AL-RAMAHI[2], J. BOTAS[2], H. Y. ZOGHBI[3];
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Abstract: The Carboxy-terminus of Hsp70-interacting protein (CHIP) is a highly conserved molecular co-chaperone and E3 ubiquitin ligase that is crucial for maintaining proteostasis through ubiquitination and degradation of misfolded and aggregated proteins. Protein misfolding underlies numerous neurodegenerative diseases, highlighting CHIP as an attractive therapeutic target with broad clinical potential. Previous studies have established CHIP's ability to mitigate protein aggregation and ameliorate disease-related phenotypes in diverse models of neurodegeneration, including Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and polyglutamine disorders. Therefore, enhancing CHIP activity represents a compelling therapeutic strategy for Spinocerebellar Ataxia Type 1 (SCA1), a progressive neurodegenerative disorder characterized by the pathological aggregation of polyglutamine-expanded ATAXIN-1 proteins. Although CHIP's neuroprotective effects have been demonstrated in other neurodegenerative contexts, its therapeutic potential in mammalian models of SCA1 and the systemic impact of moderate CHIP elevation remain unexplored. Leveraging our lab's well-established *Atxn1*$^{154Q/+}$ mouse model, which faithfully recapitulates critical human SCA1 phenotypes such as progressive motor dysfunction followed by Purkinje cell pathology and bulbar dysfunction, we aim to address these critical gaps. We generated C57BL/6J mice carrying a conditional human *CHIP-HiBiT-8xGlycine-3xFLAG* overexpression allele inserted into the

Rosa26 locus and analyzed protein lysates from brain cortex, skeletal muscle, and cardiac tissue of 3-week-old mice, observing approximately 30% CHIP overexpression in heterozygous knock-in mice relative to wild-type littermates. These CHIP-overexpressing mice appear grossly similar to wild-type animals and do not exhibit detectable developmental abnormalities or premature lethality, with the oldest mice approaching 14 months of age. Comprehensive behavioral, molecular, and histological analyses are ongoing to determine the systemic tolerability of moderate CHIP elevation and to define its capacity to influence SCA1-related pathways. These studies will evaluate whether enhancing CHIP improves proteostasis, reduces ataxin-1 aggregation, and preserves neuronal integrity. Together, these findings will provide essential foundational knowledge for developing CHIP-based disease-modifying treatments for SCA1 and other neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

Disclosures: E. Garcia: None. **E. Xhako:** None. **X. Deng:** None. **J. Kim:** None. **D.C. Chung:** None. **I. Al-Ramahi:** None. **J. Botas:** None. **H.Y. Zoghbi:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.04/W21

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: R35NS127248-04
R00NS121274-04

Title: Insights into upper limb and Purkinje cell network dysfunction in SCA1 mice

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Abstract: Spinocerebellar ataxia type 1 (SCA1) is a neurodegenerative disease that progressively impairs cerebellar function and motor coordination, ultimately leading to Purkinje cell (PC) loss. PC dysfunction in mouse models of SCA1 manifests as altered firing patterns, excitability, and plasticity. Notably, the onset of motor dysfunction occurs prior to overt PC loss, implicating PC network dysfunction as a key contributor to disease progression. A key outstanding question is how alterations in cerebellar activity drive behavioral dysfunction at the population level and across the cytoarchitecture of the cerebellar cortex. Traditional assessments of motor function in rodent ataxia models examine gross trunk and limb coordination, potentially limiting their ability to detect subtle impairments and clinically meaningful phenotypes. Here, we investigate how PC network dynamics contribute to motor dysfunction during spontaneous treadmill behavior and clinically relevant skilled reaching in male and female wild-type (WT) and *f-ATXN1*$^{[146Q/2Q]}$ SCA1 mice. PCs were selectively labeled with a PCP2-GCaMP7f virus and mice were implanted with a cranial window spanning ~13mm^2 of the dorsal cerebellar surface

for chronic widefield imaging in awake mice. At 25 weeks, PC calcium dynamics were quantified during treadmill behavior and metrics including frequency, amplitude, and correlated activity of functional PC networks were assessed. SCA1 mice exhibited disrupted calcium dynamics characterized by reduced frequency, amplitude, and correlated activity compared to their WT littermates. To assess upper limb coordination, *f-ATXN1*$^{[146Q/2Q]}$ and WT littermates were trained in a cued reach-to-grasp task and reaching kinematics were quantified using Deeplabcut and custom Matlab scripts. At 25 weeks, SCA1 mice exhibited a higher rate of failed reaches and altered kinematics including increased velocity, acceleration, and path lengths. These findings provide insight into the PC population dynamics underlying motor dysfunction and identify similar upper limb deficits in SCA1 mice and cerebellar ataxia patients.

Disclosures: A. Soles: None. **H.T. Orr:** None. **M.L. Streng:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.05/W22

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: Minnesota Office of Higher Education David J. Tomassoni ALS Research Grant Program
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Regenerative Medicine Minnesota

Title: Investigating the role of microglia and macrophages in the pathogenesis of Spinocerebellar Ataxia Type 1 with conditional knockout mouse models

Authors: *G. J. FUCHS, I. M. BROOKS, E. PARNERKAR, A. SELIMOVIC, M. CVETANOVIC;
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Abstract: Spinocerebellar Ataxia Type 1 (SCA1) is a neurodegenerative disease characterized by deficits in motor coordination, balance, and cognition. SCA1 is caused by CAG repeat expansion in the coding region of the Ataxin-1 gene (*ATXN1*), causing death of Purkinje cells in the cerebellum. Despite the observation of chronically activated microglia in SCA1 and the improvement of motor symptoms following pharmacologic immunosuppression, the role of microglial *ATXN1* remains unknown. To investigate this, mutant *ATXN1* was knocked out in microglia and macrophages using a *LYVE1*-cre mouse line and microglia exclusively using a *TMEM119*-creER^{T2} mouse line. Mice were subjected to Barnes maze, beam walk, open field, and rotarod behavioral tests at various timepoints and their cerebella were immunofluorescently

stained against ionized calcium-binding adapter molecule 1 (IBA1), a microglia marker. Preliminary analysis suggests that *LYVE1*-cre and *TMEM119*-creER^{T2} microglia will exhibit a morphology similar to wildtype microglia, marked by reduced soma volume and increased ramification, indicative of homeostasis, relative to microglia of diseased mice. These results will provide insight into the role of microglial *ATXN1* in reactive morphological phenotypes and microglia-autonomous effects in SCA1 pathogenesis with the ultimate goal of identifying potential therapeutic targets.

Disclosures: G.J. Fuchs: None. **I.M. Brooks:** None. **E. Parnerkar:** None. **A. Selimovic:** None. **M. Cvetanovic:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.06/W23

Topic: C.04. Movement Disorders Other than Parkinson's Disease

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National Ataxia Foundation, Young Investigator Award

Title: The role of ubiquitination pattern in Spinocerebellar Ataxia Type 3 (SCA3)

Authors: J. ZHOU, J. SCHMIDT, P. PEREIRA SENA, ***T. SCHMIDT**;
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Abstract: Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is the most prevalent autosomal-dominant polyglutamine (polyQ) ataxia worldwide. The disorder is caused by an expanded CAG repeat in the *ATXN3* gene, leading to a polyglutamine (polyQ) repeat expansion in the ataxin-3 protein. The polyQ expansion renders ataxin-3 prone to misfolding, aberrant protein interactions, and progressive accumulation in vulnerable neurons. The shuttling of ataxin-3 from the cytoplasm to the nucleus turned out to be a critical prerequisite for disease onset. Ataxin-3 occupies a central position in the cellular proteostasis machinery because it functions both as disease-associated substrate and as deubiquitinating enzyme (DUB). Through its enzymatic function, ataxin-3 edits preexisting ubiquitin chains rather than simply removing them, thereby reshaping their length and linkage composition. Ubiquitin is a conserved post-translational modifier that can be extended into chains with distinct linkage types encoding different cellular outcomes. Because ataxin-3 can both bind and remodel these chains, it is uniquely positioned to influence how ubiquitin signals are interpreted and how substrates are directed within the proteostasis network. In polyQ diseases such as SCA3, this network becomes progressively compromised. Misfolded ataxin-3 accumulates and can evade efficient degradation, sequester ubiquitin and proteasomal components, and impose a sustained burden on cellular clearance pathways. To address how ubiquitin linkage composition regulates ataxin-3

proteostasis, we systematically examined the effects of defined ubiquitin chain environments on ataxin-3 ubiquitination, aggregation, degradative pathway engagement, and toxicity in complementary cellular and in vivo SCA3 models. We employed a panel of ubiquitin constructs with distinct chain-forming capacities and investigated whether ubiquitin chain topology actively influences how pathogenic ataxin-3 is partitioned between proteasomal and autophagy-associated processing pathways under disease conditions. Our findings suggest that the ubiquitin chain topology influences ataxin-3 fate and that SCA3-related toxicity is not determined only by how efficiently ataxin-3 is degraded, but also by how ubiquitin signals direct ataxin-3 into different proteostasis pathways like the ubiquitin-proteasome system or autophagy-associated pathways. Thus, ubiquitin linkage composition may function not only as a degradation signal, but also as a regulatory code that shapes the intracellular fate of disease-associated proteins.

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Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.07/W24

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: Mount Sinai Seed Fund

Title: Neurodegeneration and Inflammation in a Novel Spinocerebellar Ataxia 13 Preclinical Model

Authors: *M. WU[1], J. YIN[2], J. WHITE[4], S. KHARE[4], M. GAO[5], C. M. LUTZ[6], K. ALLEN[7], H. NICK[8], M. WATERS[3];
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Abstract: BACKGROUND: Neuroinflammation is a critical pathological feature underlying neurodegenerative diseases. Spinocerebellar ataxia 13 (SCA13) is a heterogeneous ataxia with neurodegenerative and currently without effective treatment. Our prior work identified human KCNC3 gene mutations as causative for SCA13. The precise nature of the inflammation and its link to neurodegeneration in SCA13 remains elusive. METHODS: We engineered a single Kcnc3 R424H mutation (analogous to the human SCA13 KCNC3 R423H allele) into mice using CRISPR/Cas9. We performed thorough phenotypic analyses including motor function and brain segmental /cerebellar volume at multiple timepoints. We then investigated both neurodegenerative Purkinje cell (PC) loss and inflammatory responses within the cerebellum and systemically. RESULTS: At 3 and 6 months of age, the R424H mice displayed profound neurological motor dysfunction, including high-frequency tremor, aberrant gait, and a decreased

latency to fall. Electrophysiology revealed dysregulated spontaneous firing in PCs. Pathological examination confirmed progressive PC degeneration and cerebellar atrophy. Critically, we observed a pronounced activation of microglia and astrocytes within the cerebella of R424H mice. Pearson correlation analyses highlighted a strong inverse correlation between the number of surviving PCs and markers of inflammatory activation. CONCLUSIONS: Our R424H mice establish a novel model of brain hypoplasia and neurodegeneration caused by dysfunction of a voltage-gated potassium channel mimicking SCA13R423H, exhibiting significant motor deficits, prominent PCs loss, cerebellar inflammation, and atrophy. This study suggests that the aberrant activation of inflammatory immune cells, notably astroglia and microglia, is associated with PC demise in the cerebellum. We propose that this abnormal neuroinflammation plays a significant and potentially aggressive role in driving the progression of neurodegeneration in SCA13.

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Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

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Program #/Poster #: PSTR307.08/W25

Topic: C.04. Movement Disorders Other than Parkinson's Disease

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Title: Loss of phospholipid asymmetry induces microglia-dependent cerebellar neurodegeneration

Authors: *S. TOKUNAGA[1], M. KAWASE[1], H. SHAWKI[2], C. MIYAJIMA[3], J. OMI[5], O. S. CHAPMAN[4], J. AOKI[6], D. KAWAUCHI[4], H. OISHI[2], M. HATTORI[1];
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Abstract: Phosphatidylserine (PS) externalization and its recognition by glial PS receptors are critical processes regulating neuronal homeostasis. Phospholipid flippases maintain PS asymmetry by transporting PS from the outer to the inner leaflet of the plasma membrane. In the central nervous system, ATP8A1 and ATP8A2 are major flippases. Loss of function of ATP8A2 leads to cerebellar ataxia, mental retardation, and disequilibrium syndrome (CAMRQ). However, whether disruption of PS asymmetry contributes to neurodegeneration remains unclear. Here, we show that deficiency of the flippases ATP8A1 and ATP8A2 causes progressive cerebellar neurodegeneration and motor dysfunction in mice. ATP8A1/ATP8A2 double knockout (DKO)

mice exhibited abnormal hindlimb clasping reflexes and ataxic gait. Neurodegeneration was predominantly observed in cerebellar white matter and cerebellar nuclei and progressed from postnatal day (P) 14 to P21 without overt Purkinje cell (PC) loss. Bulk RNA-seq and CIBERSORTx deconvolution analyses identified early microglia-associated changes in ATP8A1/ATP8A2 DKO cerebella. Although no overt neurodegeneration or major transcriptomic differences were detected at P0, the deconvolution analysis indicated an increase of microglial fraction in ATP8A1/ATP8A2 DKO mice. At P14, ATP8A1/ATP8A2 DKO cerebella showed upregulation of multiple microglia-enriched genes. Consistent with these findings, ATP8A1/ATP8A2 DKO mice exhibited increased microglial density. We hypothesized that microglia are pathologically activated and that excessive microglial engulfment of PCs contributes to neurodegeneration. To test this, we examined whether deletion of one of microglial PS receptors TREM2 could ameliorate neurodegeneration in ATP8A1/ATP8A2 DKO mice. We generated ATP8A1/ATP8A2/TREM2 triple knockout (TKO) mice and found that deletion of TREM2 partially ameliorated cerebellar neurodegeneration and hindlimb clasping reflexes. Notably, the proportion of homeostatic P2RY12-positive microglia was increased in ATP8A1/ATP8A2/TREM2 TKO mice. These findings demonstrate that loss of ATP8A1 and ATP8A2 disrupts PS asymmetry in PC axons and induces pathological microglial activation associated with cerebellar neurodegeneration and that modulation of microglial PS receptor signaling pathways may represent a therapeutic strategy for cerebellar neurodegenerative diseases.

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Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.09/W26

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Title: Understanding variant-specific vulnerability of cerebellar granule neurons in TUBB4A-related leukodystrophy

Authors: *N. SURVE[1,2], A. BHAGAVATULA[1], P. NAPIT[3], S. SASE[4], A. VANDERVER[1,2]; [1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]The Children's Hosp. of Philadelphia, Philadelphia, PA; [4]Children's Hosp. of Pennsylvania, Philadelphia, PA

Abstract: Microtubules, composed of α-β tubulin heterodimers, are essential for neuronal function, intracellular trafficking, and myelination. Mutations in tubulin genes cause a range of neurological disorders, including leukodystrophies—rare genetic diseases involving abnormalities in brain white matter. Heterozygous missense mutations in the ***TUBB4A*** gene

result in ***TUBB4A*-related leukodystrophy (*TUBB4A*-LD),** with a clinical spectrum from isolated hypomyelination to severe **Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC)**. Milder *TUBB4A*-LD variants result in isolated hypomyelination with no cerebellaratrophy. Conversely, the severe *TUBB4A*^{D249N} and *TUBB4A*^{R262H} variants exhibit progressive cerebellar atrophy, often resulting in early childhood mortality. While cerebellar granule neuron (CGN) loss is a hallmark of H-ABC, the impact of the toxic gain-of-function *TUBB4A* variants on CGN loss remains unclear. Notably, previous studies from our lab show that antisense oligonucleotide (ASO)-mediated *Tubb4a* suppression ameliorates the hypomyelination phenotype but fails to prevent CGN loss, highlighting independent, unresolved mechanisms of neurodegeneration. Our studies employ novel mouse models to examine the impact of specific *TUBB4A*-LD variants on CGNs, revealing differences in neuronal vulnerability. In addition to profound CGN loss, we also observe Purkinje cell abnormalities, including axonal torpedoes, suggesting disruption of cerebellar circuit integrity. Using high-resolution imaging and biochemical approaches, we assess alterations in microtubule dynamics and organelle trafficking in primary murine CGNs. Our study elucidates the cellular mechanisms underlying selective CGN vulnerability, providing a framework to guide therapeutic strategies for *TUBB4A*-LD and related tubulinopathies.

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Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.10/W27

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: RM1NS143850

Title: Structural insights into frataxin gene-targeted histone H3K27 demethylase KDM6B substrate recognition on heterochromatin in Friedreich’s ataxia

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Abstract: Friedreich’s Ataxia (FRDA) is a genetic neurodegenerative disease that has an incidence of 1:50,000, with disruption of muscle coordination, impaired speech, and cardiomyopathy. Currently, there is no cure for the disease. FRDA is caused by the silencing of the frataxin (*FXN*) gene through heterochromatinization on the expanded GAA repeats at the gene, featuring a high level of trimethylation of histone H3 lysine 27 (H3K27me3). Previous results from our group showed that the inhibition of H3K27 methyltransferases can promote GAA repeat instability, suggesting that it is possible to navigate the instability of the expanded

GAA repeats towards contraction by modulating histone H3K27 methylation for FRDA treatment. We hypothesize that demethylation of H3K27me3 on the expanded GAA repeats at the *FXN* gene can lead to repeat contraction via base excision repair (BER) in FRDA. To test this, we developed a CRISPR/dCas9-mediated *FXN* gene-targeted demethylation of H3K27me3 system on the expanded GAA repeats in FRDA by dCas9-H3K27 demethylases KDM6A and KDM6B fusion proteins. To understand the molecular mechanisms underlying the substrate recognition of *FXN* gene-targeted KDM6A and KDM6B in the heterochromatin of the expanded GAA repeats in FRDA, using computational modeling and the AI tool AlphaFold3, we created a model of CRISPR/dCas9-KDM6B fusion protein with a guide RNA (gRNA) located at 3 bp downstream of the GAA repeats of the *FXN* gene within two nucleosomes containing a H3K27me3 residue wrapped by 45 GAA repeats. The results showed that the two nucleosomes were compacted in a heterochromatin fashion. Surprisingly, we found that gRNA basepaired with the DNA template was predominantly mediated by the last four nucleotides at the 3'-end, allowing for sufficient *FXN* gene-targeted delivery of the dCas9-KDM6B. We then demonstrated that the dCas9-KDM6B fusion protein tightly bound to H3K27me3 by evaginating the residue into its catalytic center in the heterochromatic nucleosomes wrapped by 45 GAA repeats. Moreover, we showed that the dCas9-KDM6B fusion protein bound to the nucleosome at its edge, allowing KDM6B to readily access its substrate the methyl groups, without being interfered with nucleosome discs. Our results provide the first visualization of substrate recognition by *FXN* gene-targeted dCas9-KDM6B in the heterochromatic nucleosomes in FRDA. Also, this allows us to further establish a novel platform to design and engineer human KDM6B and KDM6A to their highest efficiency, thereby opening a new avenue for the effective treatment of FRDA and other repeat expansion diseases.

Disclosures: L. Bertolami: None. **Y. Liu:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.11/Web Only

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Title: Aging-related upregulation of piwi-piRNA pathway genes in brain and head tissues of Drosophila melanogaster: a computational analysis

Authors: *S. JHA[1], N. M J[2];
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Abstract: Aging is associated with known hallmarks including genomic instability and transposon derepression. In a recent study, we found that *DDX helicases* exhibit differential expression patterns in skeletal muscles during aging in multiple species (Nishanth and Jha 2026, Biogerontology 27 (1), 35). We followed-up this work, to analyse whether this differential expression is also seen in other tissues during aging, using publicly available transcriptome data

pertaining to *Drosophila melanogaster*. We found two *DDX helicases*, *SoYb*, *BoYb*, and an interactor of SoyB, *Vret*, to show consistent differential expression in aged tissues. These genes are known to encode proteins involved in the Piwi-piRNA pathway (Salgania et al. 2025; Nucleic Acids Research, 53(19)). Hence, we further explored the expression levels of all known Piwi-piRNA pathway genes in the considered datasets. As a result, we found that a number of genes of this pathway exhibit differential expression patterns across datasets from multiple tissues including the head, brain, gut, and fat body, during aging. Notably, *Aub*, *Qin*, *Krimp*, *Spn-E*, *Vret*, and *Piwi*, showed lower transcript levels (downregulated) in brain and head tissues, and higher expression (upregulated) in fat body and thorax tissues of younger flies. The increased expression levels of multiple piRNA pathway genes in aged head and brain tissues may reflect an enhanced need for the Piwi-piRNA pathway function/activity with aging. The established function of the Piwi-piRNA pathway is repression of transposable elements (TEs), especially in germline (Ozata et al. 2019; Nature Reviews Genetetics 20 (2): 89-108). The non-germline functions of this pathway are only beginning to be understood. The present work suggests age-dependent differential expression of the Piwi-piRNA system in somatic tissues. Hence, this study offers insights into the potential involvement of this pathway in molecular regulation of aging. Further experimental studies in this regard would advance our understanding of aging-related post-transcriptional gene regulatory processes involving TEs and their silencing.

Disclosures: S. Jha: None. **N. M j:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

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Program #/Poster #: PSTR307.12/W28

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: NIH Grant 1R21EB032059

Title: Towards optimized sensory electrical stimulation-based wrist tremor suppression in essential tremor disease

Authors: *V. GANESH[1], X. XUE[1], N. SHARMA[2];
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Abstract: Involuntary motions from tremor impact the daily activities of the approximately 25 million individuals diagnosed with essential tremor (ET) disease. The medication and surgeries used to treat ET can be limited in efficacy and carry associated risks. A non-invasive alternative is sensory electrical stimulation (SES), in which low-level current activates sensory neurons to suppress tremors. For wrist tremors, common electrode sites are the flexors and extensors, which may not affect the pronator and supinator downstream. Furthermore, prior work has shown the impact of SES amplitude and inner frequency on tremor suppression efficacy, yet burst

frequency remains largely unexplored. In this work, we build on existing tremor suppression SES paradigms by targeting individual major forearm muscles during stimulation while investigating the relative efficacies of various SES burst frequencies. We collected data from 3 individuals with ET. For each trial, the subject held a tremor-eliciting posture for 70 seconds with SES applied for the last 45 seconds, and tremor suppression ratios (TSR) were calculated by comparing inertial data collected during stimulation to baseline. Electrodes were placed in either the conventional 2-SES or 6-SES (Fig. 1A) configurations. For both, we performed 5 trials with each SES burst frequency of 2, 4, 6, 8, 10, and 12 Hz, which encompass the range of ET frequencies. Representative results for subject S1 are in Fig. 1B. All subjects had their best mean frequency-specific TSRs (S1: 69.4±14.2%, S2: 32.3±16.1%, S3: 85.2±17.9%) with 6-SES at the respective burst frequencies of 4, 6, and 12 Hz. ANOVA analysis ($p<0.05$) for S1 and S3's 6-SES data and notably high TSR's support burst frequency optimization during SES-based wrist tremor suppression. 6-SES yielded a mean increase of 33.3±26.6 in TSR over 2-SES at the best burst frequency, indicating the value of targeting the pronator and supinator during SES. Overall, our results reinforce the viability of SES-based tremor suppression in ET and encourage further study of subject-specific optimization of SES protocols.

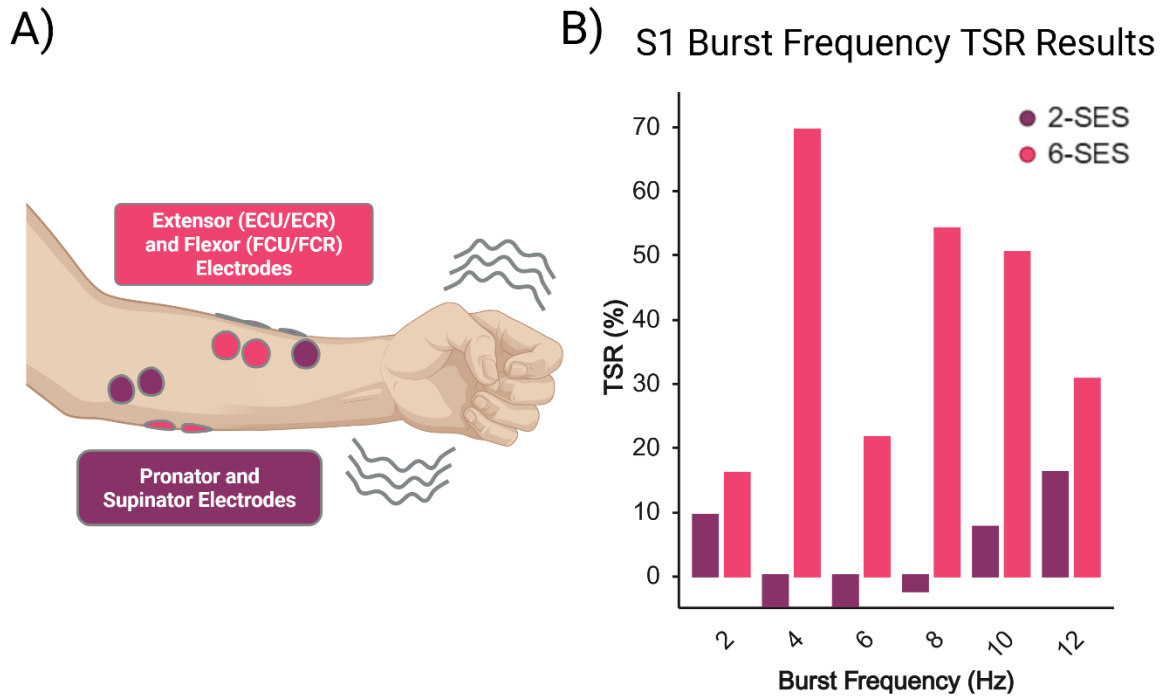


Figure 1: A) 6-SES Electrode Diagram B) S1 Burst Frequency Sweep Results

Disclosures: V. Ganesh: None. **X. Xue:** None. **N. Sharma:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.13/W29

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Title: Pharmacological characterization of the harmaline mouse model of essential tremor using integrated multimodal biomarker profiling

Authors: *N. VAUTRELLE, M. VILLALBA, B. CARABALLO, C. ALLIOUX, C. DUMONT, E. GRONLIER, C. HABERMACHER, J. VOLLE;
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Abstract: Essential tremor (ET) is the most common adult-onset movement disorder, affecting approximately 1% of the general population. Despite its high prevalence, ET pathophysiology remains incompletely understood, and available pharmacological treatments are largely empirical, with variable efficacy and tolerability. Preclinical approaches integrating central neurophysiological measures with peripheral tremor readouts are therefore essential to improve translational evaluation of candidate therapies.
Harmaline, a β-carboline alkaloid, is widely used to induce an acute pharmacological model of ET in rodents. By activating inferior olive neurons, it produces synchronous rhythmic activity that entrains the cerebello-thalamo-cortical circuit, resulting in action tremor. In mice, tremor oscillations occur within 8-14 Hz, closely mirroring the oscillatory characteristics of human ET. In this study, we performed a pharmacological characterization of the harmaline mouse model by combining electroencephalography (EEG) with piezoelectric-based quantification of peripheral tremor. Across multiple cohorts, we evaluated nine mechanistically distinct compounds: agents used clinically in ET management (propranolol, gabapentin, alprazolam), selective T-type calcium channel inhibitors in clinical development (ulixacaltamide, suvecaltamide), and pharmacological probes targeting ET-relevant pathways (eslicarbazepine, ethanol, caffeine, ganaxolone). Peripheral and central biomarkers were assessed simultaneously: motion power ratio for peripheral tremor, EEG power spectral density (40-60 Hz) in motor cortex and cerebellum, and cortico-cerebellar coherence at tremor-related frequencies.
Harmaline reliably induced action tremor accompanied by enhanced central oscillatory activity. Most anti-tremor compounds reduced peripheral tremor and attenuated central oscillatory power but modulated coherence in a complex, time-dependent manner, revealing a consistent dissociation between biomarker modalities. T-type calcium channel inhibitors produced the most robust peripheral tremor suppression, with ulixacaltamide and suvecaltamide displaying a distinctive biphasic coherence response that distinguished their mechanistic profile from other compounds.
Together, these findings demonstrate that integrated central and peripheral biomarker profiling reveals mechanism-specific pharmacological signatures not captured by single-endpoint approaches. This work establishes a pharmacological reference dataset and translational framework for preclinical drug evaluation in ET.

Disclosures: N. Vautrelle: A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **M. Villalba:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **B. Caraballo:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **C. Allioux:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **C. Dumont:** A. Employment/Salary (full or part-time):;

SYNAPCELL SAS. **E. Gronlier:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **C. Habermacher:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS. **J. Volle:** A. Employment/Salary (full or part-time):; SYNAPCELL SAS.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.14/W30

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Support: NIH KO8

Title: Dissecting the pathological mechanisms behind BORCS5 variants

Authors: *T. BRANCO[1], G. MINAKAKI[1], I. SANTIAGO-MARRERO[1], T. ABRAMOVA[1], J. N. SAVAS[1], M. SCHWAKE[2], D. KRAINC[1], N. MENCACCI[1];
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Abstract: BORCS5 encodes a subunit of the BORC complex essential for anterograde lysosome transport. BORCS5 mutations cause a spectrum of devastating neurological disorders. While truncating variants abolish BORCS5 protein levels and thwart anterograde lysosome movement, the missense variants R95Q and H99P preserve lysosome trafficking. Nevertheless, both truncating and missense variants disrupt lysosome activity. How BORCS5 and its pathogenic missense variants contribute to lysosomal dysfunction and neuronal pathology remains unknown. To characterize the pathological mechanisms underlying BORCS5 missense variants, we generated: (1) HeLa knock-in (KI) for R95Q or H99P; (2) BORCS5 KO HeLa stably re-expressing wild-type (WT) BORCS5; (3) BORCS5 KO HeLa stably expressing KBS-LAMP1, which forces kinesin to lysosomes independently of BORC; and (4) BORCS5 KO and R95Q/H99P KI iPSCs. Whereas BORCS5 KO caused perinuclear clustering of lysosomes and elevated LC3-II levels in HeLa cells, R95Q and H99P KI did not impact on lysosome distribution or LC3-II levels. However, all three genotypes — KO, R95Q, and H99P — exhibited reduced lysosomal proteolysis, confirming that missense variants impair lysosome function despite preserving anterograde movement. To further dissociate transport from function, we expressed BORCS5-WT or KBS-LAMP1 in KO cells. Both constructs restored anterograde movement; however, only BORCS5-WT rescued LC3-II levels and recovered cathepsin B (CTSB) and glucocerebrosidase (GCase) protein levels, indicating that restoring lysosome positioning alone is insufficient to correct lysosomal dysfunction upon BORCS5 loss. In iNeurons, BORCS5 KO abrogated lysosome trafficking, while R95Q/H99P KI iNeurons showed near-complete recovery of axonal lysosome distribution. BORCS5 KO iNeurons exhibited lysosomal dysfunction, including reduced GCase activity, decreased CTSB and GCase protein levels, elevated LC3-II and LAMP1/2, and autophagosome accumulation by TEM — consistent with impaired autophagosome clearance. LysoIP confirmed depletion of CTSB and GCase within endolysosomal fractions of KO iNeurons. Thus, BORCS5 depletion and bi-allelic variants

lead to lysosomal dysfunction. BORCS5-depleted cells exhibit reduced lysosomal proteolysis and decreased CTSB and GCase levels and activity, which cannot be rescued by restoring anterograde lysosome movement, indicating that BORCS5 plays a role in lysosome homeostasis beyond its canonical function in anterograde transport.

Disclosures: T. Branco: None. **G. Minakaki:** None. **I. Santiago-Marrero:** None. **T. Abramova:** None. **J.N. Savas:** None. **M. Schwake:** None. **D. Krainc:** None. **N. Mencacci:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.15/X1

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Title: 55 Hz versus 185 Hz STN-DBS produces dissociable PPN oscillatory responses in pediatric dystonia

Authors: *Y. SUN[1], A. SEYYED MOUSAVI[2], T. D. SANGER[3];
[1]Univ. of California, Irvine, Irvine, CA; [2]Uni. of California Irvine, Irvine, CA; [3]Res., Children's Hosp. of Orange County, Orange, CA

Abstract: Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) is an established treatment for pediatric dystonia. In adult Parkinson's disease, adjusting STN-DBS from high-frequency (185Hz) to low-frequency (55-60Hz) modulates gait and axial symptoms via descending brainstem networks. Whether similar frequency-dependent modulation exists in pediatric dystonia patients, particularly via the pedunculopontine nucleus (PPN), a brainstem locomotor center receiving dense subthalamic projections, remains unknown.
We compared the acute effects of 55Hz versus 185Hz STN stimulation on PPN local field potentials (LFPs) in pediatric dystonia patients during a 1-2 week postoperative lead externalization period in the Neuromodulation Monitoring Unit (NMU). AdTech MM16C depth leads were temporarily implanted into multiple targets including GPi, STN/SNr, Vo, VIM, and PPN, enabling stimulation through macro-contacts while simultaneously recording local brain signals via micro-contacts. Stimulation amplitude was 1.5V or 3V based on patient tolerance. Both conditions were tested within the same session to minimize day-to-day variability. Active channels were identified using dual-validation (anatomical localization via imaging co-registered to preoperative MRI, plus evoked potential verification). Power spectral density (PSD) was computed and normalized to each condition's pre-stimulation baseline (10*log10[On-Stim/Baseline]). The broadband spectral trend was calibrated using the high-frequency band (65-160 Hz) to isolate frequency-specific modulations. Power was analyzed in 1-50 Hz across delta, theta, alpha, and beta bands using non-parametric bootstrap resampling (1,000 iterations) with FDR correction.
Across all subjects, STN185 produced greater PPN power than STN55 in low-frequency bands.

Most subjects showed STN55 suppression of PPN activity below baseline while STN185 produced enhancement. Spectral profiles showed STN185-driven enhancement was most prominent below 30 Hz, with additional peaks in the alpha/low-beta range (15-25 Hz) in some subjects. These findings suggest frequency-specific STN-PPN network engagement in pediatric dystonia. Adjusting STN-DBS frequency may selectively target downstream brainstem networks involved in postural and motor control, potentially enabling personalized stimulation strategies.

Disclosures: Y. Sun: None. **A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

PSTR307: Ataxias and Dystonia

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR307.16/X2

Topic: C.04. Movement Disorders Other than Parkinson's Disease

Title: Variation-tolerant movement classification in continuous ice dance motion streams using sliding normalized template matching

Authors: *A. YING[1], S. YING[3], Y. TARUI[4], A. JOYCE[2], A. JOYCE[5], V. YE[5], N. YING[5], C. JOYCE[2], M. BRAMANTE[6], S. H. YING[7];
[1]DeeperEdge, Cambridge, MA; [2]DeeperEdge, Mansfield, MA; [3]Res. Intern, Deeper Edge, Cambridge, MA; [4]Deeper Edge, Newton, MA; [5]Deeper Edge, Cambridge, MA; [6]Cambridge Col., Boston, MA; [7]Neurol., MEEI, Cambridge, MA

Abstract: Background: Clinical management and trials for neurological movement disorders would benefit from objective methods that classify repeated movements while allowing for normal variation in execution. Ice dance provides a useful model because pattern dances are standardized, but real performances vary across individuals and repetitions in amplitude, morphology, and timing. A practical movement-recognition algorithm should not require each movement to match an idealized template at one exact frame. We tested whether sliding normalized template matching can classify movements in a continuous stream while tolerating individual variability and early or late execution.
Methods: Full-body wearable IMU data were analyzed from Dutch Waltz pattern dances. Movement templates were correlated against a continuous trace using FFT-based normalized template matching across motion channels. Unlike fixed-window root mean square distance (RMSD), the algorithm searched all lags, allowing the detected peak to occur at the time of strongest movement-template similarity rather than at a preset frame. Related variants were merged into movement families, allowing biomechanically similar executions to share a label. Candidate detections were converted to a noise-baseline-normalized signal-to-noise score and assigned to the class with the highest local score.
Results: In a cross-performance comparison, the algorithm classified movements directly from a continuous Dutch Waltz stream. It detected peaks near all 80 expected step starts and correctly classified 79 of 80 steps using merged movement-family labels. Detections were not required to

occur at the annotated start frame; instead, the strongest match could shift locally, with a mean offset of -2.01 frames, median offset of -1 frame, mean absolute offset of 11.08 frames, and maximum absolute offset of 42 frames. Thus, the algorithm identified movements even when the performed step did not align perfectly with the expected start.
Conclusion: Sliding normalized template matching classified repeated Dutch Waltz movements in a continuous IMU stream while tolerating variation in timing and execution. By searching across time, normalizing shape similarity, and grouping related variants, the algorithm can recognize a movement even when the subject does not perform it at the expected moment. This human-variation-tolerant approach may support wearable movement recognition systems intended to generalize across individuals, repetitions, and clinically relevant deviations from ideal timing.

Disclosures: A. Ying: None. **S. Ying:** None. **Y. Tarui:** None. **A. Joyce:** None. **A. Joyce:** None. **V. Ye:** None. **N. Ying:** None. **C. Joyce:** None. **M. Bramante:** None. **S.H. Ying:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.01/X3

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

Title: Accelerated iPSC-derived Alzheimer’s disease model drives equimolar 3R/4R tau expression and tau hyperphosphorylation

Authors: A. VETELEANU[1], S. BARBARIA[2], A. TURNER[1], S. SALIC-HAINZL[2], ***T. OOSTERVEEN**[1], W. BERNARD[1];
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Abstract: The microtubule-associated tau protein is encoded by the MAPT gene and is involved in stabilising microtubules, thereby controlling axonal outgrowth. The MAPT transcript can be alternatively spliced, generating six main isoforms in the human brain encoding three (3R) or four (4R) carboxy-terminal repeat domains that have different affinities for microtubules. Although tau itself is a highly soluble protein, mutations affecting its phosphorylation status, or the 3R/4R ratio, can cause tau aggregation. These tauopathies are associated with different diseases and are mainly caused by mutations in the repeat domains. Alzheimer's disease (AD) is a 3R/4R tauopathy in which tau aggregates consist of both 3R and 4R tau protein. For this reason, it has been challenging to model AD, as the mouse brain almost exclusively expresses the 4R tau isoform and iPSC-derived neurons predominantly express the 3R variant unless cultures are maintained for extensive periods of time.
To generate a reliable and practical AD model, we used opti-ox deterministic programming to generate ioGlutamatergic Neurons harbouring a homozygous S305N mutation, which is known to drive the inclusion of exon 10 which encodes the fourth repeat in the 4R isoform. In addition,

ioGlutamatergic Neurons MAPT S305N/S305N were generated with either a heterozygous or homozygous P301S mutation, which is also located in exon 10 and can cause tau hyperphosphorylation. qPCR analysis showed that the ioGlutamatergic Neurons MAPT S305N/S305N cultured for 30 days have near-equimolar amounts of 3R and 4R isoforms, while wild-type cells express almost no 4R. Western blotting further confirmed the presence of significant amounts of 4R tau and showed hyperphosphorylation of the tau protein in comparison to wild-type cells. Interestingly, at this culture time, the addition of the P301S mutation on top of the S305N mutation did not further increase the phosphorylation status of the tau protein. Immunocytochemistry analysis confirmed the Western blot findings, as we observed tau hyperphosphorylation and increased levels of 4R relative to the 3R isoform in the day 30 ioGlutamatergic Neurons MAPT S305N/S305N (with or without P301S) cultures. ioGlutamatergic Neurons MAPT mutants are now being further characterised by studying the phosphorylation status of specific tau amino acid residues and the formation of tau aggregates. Overall, our data show that our MAPT mutant ioGlutamatergic Neurons have critical features required for AD modelling, including the expression of equimolar ratios of the 3R and 4R isoforms and the presence of hyperphosphorylated tau protein.

Disclosures: A. Veteleanu: A. Employment/Salary (full or part-time):; bit.bio. **S. Barbaria:** A. Employment/Salary (full or part-time):; bit.bio discovery. **A. Turner:** A. Employment/Salary (full or part-time):; bit.bio. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time):; bit.bio discovery. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.02/X4

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

Support: NIH RO1/5R01NS136448-03
CurePSP/693-2024-03-Urso

Title: Tau Expression Increases Vulnerability to Cellular Stress but Is Essential for the Maturation of Human Stem Cell Derived Neurons

Authors: *B. DOLATYAR[1], N. FIROUZSHAHI[2], D. GONZÁLEZ[4], J. GLYKYS[5], M. M. HEFTI[3];
[1]Univ. of Iowa, IOWA CITY, IA; [2]Neurosci., [3]Univ. of Iowa, Iowa City, IA; [4]Univ. Politécnica De La Zona Metropolitana D, Guadalajara, Mexico; [5]Pediatrics and Neurol., The Univ. of Iowa, Iowa City, IA

Abstract: Tau protein is a key contributor to neurotoxicity in the adult and aging brain. However, its strong evolutionary conservation suggests an important, yet poorly understood, role during early development. Findings from rodent models have been inconsistent and are difficult to interpret due to differences in tau amino acid sequence, while human studies have largely focused on its involvement in neurodegeneration. Here, we present a comprehensive analysis of developmental phenotypes in human tau knockout neurons.
Human embryonic stem cells (hESCs) were differentiated into mixed dorsal forebrain cultures, corresponding to second-trimester human fetal neurons. Cellular phenotypes were characterized using Western blotting, quantitative PCR, immunocytochemistry, electrophysiology, lentiviral transduction, and RNA sequencing. Image quantification was performed using MATLAB and ImageJ.
After 14 days of differentiation, tau knockout neurons exhibited reduced TUJ1 staining ($p = 0.004$), indicating a loss of neuronal processes, while MAP2 staining remained unchanged, suggesting selective impairment of axons rather than dendrites. Synaptic analysis revealed decreased staining and increased somatic localization of PSD-95 ($p = 0.007$), with similar patterns observed for synaptophysin, although total protein levels were unchanged. These deficits were rescued by expression of 0N3R-RFP tau. Tau knockout neurons also showed broader maturation deficits, including reduced neuronal number ($p = 0.0395$), increased input resistance (1154 MΩ vs. 386 MΩ, $p = 0.0053$), and prolonged membrane time constant (62.96 ms vs. 34.6 ms, $p = 0.0335$). RNA sequencing identified 698 downregulated and 1169 upregulated genes, with downregulated genes enriched for pathways related to neuronal differentiation. Tau knockout neurons also displayed increased resistance to three common hypoxic stress conditions compared with wild-type neurons, as assessed by multiple viability assays. Given the differences between mouse and human results, we then knocked a human-specific N-terminus region into the mouse Tau gene and observed significantly higher levels of Tau both *in vivo* and *in vitro.*
These findings demonstrate that tau is critical for the maturation and synaptogenesis of human neurons, highlighting a role that may not be fully recapitulated in rodent systems. This previously underappreciated developmental function of tau provides new insight into mechanisms relevant to Alzheimer's disease and other tauopathies. The mechanisms by which tau regulates transcription remain unclear, warranting further investigation.

Disclosures: B. Dolatyar: None. **N. Firouzshahi:** None. **D. González:** None. **J. Glykys:** None. **M.M. Hefti:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.03/X5

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

Title: Robust iPSC-Derived Models of α-Synuclein, TAU, and TDP-43 Aggregation to Accelerate Therapeutic Development.

Authors: J. KOEPKE[1], L. SMIT[2], J. LAMB[3], B. SAMSON-COUTERIE[4], ***S. JAIN**[1]; [2]Discovery Technol., [1]Ncardia, Leiden, Netherlands; [3]Ncardia, Lein, Netherlands; [4]Discovery Technologies, Ncardia, Leiden, Netherlands

Abstract: Since Alois Alzheimer's discovery of amyloid plaques over a century ago, the accumulation and aggregation of misfolded proteins have been recognized as central hallmarks of neurodegenerative disorders. In Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD), the misfolding of TAU, α-synuclein, or TDP-43 leads to progressive neuronal dysfunction and degeneration. Despite these advances in understanding disease pathology, translation into effective therapies has been hindered by the lack of predictive, human-relevant preclinical models. We have developed a suite of human induced pluripotent stem cell (iPSC)-derived neuronal models that recapitulate key aspects of neurodegenerative disease biology, enabling mechanistic studies and therapeutic evaluation across indications. Robust in vitro assays for synucleinopathies (PD), tauopathies (AD/FTD), and ALS/FTD (TDP-43 proteinopathy) were established using disease-relevant neuronal subtypes in mono and glial co-cultures. These physiologically relevant platforms provide clinically translatable readouts and are amenable to all stages of the drug discovery process, from hit identification through lead optimization. In dopaminergic neuron cultures (iPSC-CN), exposure to recombinant pre-formed fibrils (PFFs) of α-synuclein and TAU induced aggregation and phosphorylation (pS129 α-syn, AT8-pTAU). High-content imaging quantified aggregate burden, distribution, and co-localization with pathological markers. Pharmacological modulators of protein degradation showed concentration-dependent effects on aggregate size and count, demonstrating assay sensitivity to therapeutic modulation. In parallel, iPSC-derived motor neurons (iPSC-MN) harboring ALS-linked mutations displayed TDP-43 mislocalization, aggregation, and the human-specific mis-splicing of STMN2, alongside electrophysiological impairments. These phenotypes enabled evaluation of candidate compounds targeting TDP-43 pathology and functional neuronal recovery. Together, these platforms represent a scalable, human-relevant approach to model disease pathology, quantify neurotoxicity, and evaluate therapeutic efficacy across multiple neurodegenerative diseases. By combining high-content imaging, molecular biomarkers, and functional electrophysiology, our Neurotox assays provide predictive insights into disease mechanisms and drug response, supporting the development of effective neuroprotective therapies while reducing reliance on animal models.

Disclosures: J. Koepke: None. **L. Smit:** None. **J. Lamb:** None. **B. Samson-Couterie:** None. **S. Jain:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.04/X6

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

Support: Pew Innovation Fund
UBACyT
Alzheimer's Association (25AARG-1414032)

Title: Tau mutations differentially impair lysosomal axonal transport, AIS location and spontaneous calcium signaling in patient-derived glutamatergic neurons.

Authors: *C. GAGUINE[1], C. ARNAIZ[2], M. HOLUBIEC[3], M. GARCIA[3], J. BIANCHELLI[2], S. A. ROMANO[4], M. AVALE[5], T. L. FALZONE[6];
[1]Inst. de Investigaciones en Ingeniería Genética y Biología Mol. (INGEBI-CONICET) and Inst. de Investigación en Biomedicina de Buenos Aires - Inst. Partner de la Sociedad Max Planck (IBioBA-MPSP-CONICET), Buenos Aires, Argentina; [2]IBioBA (CONICET), Buenos Aires, Argentina; [3]IBCN-UBA-CONICET, Buenos Aires, Argentina; [4]Inst. de Investigación en Biomedicina de Buenos Aires (IBioBA)-CONICET-Partner Inst. of the Max Planck Society, Ciudad Autónoma de Buenos Aires, Argentina; [5]INGEBI-CONICET, Buenos Aires, Argentina; [6]IBioBA (CONICET) and FMED-UBA, Buenos Aires, Argentina

Abstract: Tauopathies are neurodegenerative diseases characterized by abnormal Tau protein accumulation, leading to neuronal dysfunction, cell death, and dementia. Over 60 mutations in *MAPT*, the gene encoding Tau, have been linked to pathological aggregation, microtubule instability, organelle trafficking defects and synaptic dysfunction. A hallmark of tauopathies is selective neuronal vulnerability, with excitatory neurons proposed as particularly susceptible in primary tauopathies and Alzheimer's disease. Therefore, we aim to evaluate the impact of different *MAPT* mutations over morphological and functional parameters in glutamatergic human derived neurons.
Here, we generated patient-derived iPSCs glutamatergic neurons using a genetic induction protocol to investigate phenotypes associated with V337M and R406W mutations.
We assessed axonal transport by lysosomal trafficking in highly polarized neuronal cultures using live-cell fluorescence imaging. Interestingly, V337M mutation significantly reduced the proportion of static lysosomes and increased the retrograde proportion without changing the anterograde. Yet, R406W neurons showed no changes in lysosomal proportions relative to their isogenic controls. Both V337M and R406W neurons exhibited altered distributions of lysosome segmental velocities, with V337M neurons showing increased in both anterograde and retrograde segmental velocities, whereas R406W neurons lead to decreased retrograde segmental velocities and increased anterograde segmental velocities relative to control.
As changes in Tau have been implicated in alterations in neuronal electrical activity, we examined the positioning of the axon initial segment (AIS). Interestingly, we observed changes in AIS location in V337M and R406W neurons relative to their respective controls. Moreover, AIS establishment was reduced in R406W neuron cultures compared with their isogenic control.
To further characterize neuronal physiology, we evaluated calcium dynamics. Fluorescent imaging experiments revealed a reduction in amplitude and frequency of spontaneous calcium signals in V337M neurons, suggesting electrophysiological impairment in these mutants. However, no differences were observed in R406W neurons.
Overall, these findings reveal that V337M and R406W mutations differentially disrupt axonal transport and AIS location, while V337M additionally impairs calcium signaling, highlighting mutation-specific phenotypes in human glutamatergic neurons. These results provide a valuable

framework to consider in the development of cell-type-specific therapeutic strategies for tauopathies.

Disclosures: C. Gaguine: None. **C. Arnaiz:** None. **M. Holubiec:** None. **M. Garcia:** None. **J. Bianchelli:** None. **S.A. Romano:** None. **M. Avale:** None. **T.L. Falzone:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.05/X7

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

Support: RF1NS143015
Roy J. Carver Charitable Trust

Title: Atypical amygdala-predominant tau pathology in a human brain bank cohort

Authors: *H. R. WILLIAMSEN, M. L. HUNTER, M. M. HEFTI, K. L. FIOCK;
Pathology, Univ. of Iowa, Iowa City, IA

Abstract: Tau pathology in neurodegenerative disease typically follows a predictable anatomical progression pattern involving limbic and cortical structures. Although the amygdala is frequently affected in early tauopathy, isolated tau pathology restricted to the amygdala without hippocampal involvement is poorly characterized. We examined phospho-tau immunoreactivity across four phosphoepitopes in postmortem human brains with tau pathology confined to the amygdala. Fixed human brain tissue from 37 postmortem cases was procured by the Iowa Neuropathology Resource Laboratory through family consented donations and Iowa State Medical Examiner autopsies. Amygdala-restricted cases were identified from individuals without known neurodegenerative disease to reduce potential confounding from established tauopathies. Immunohistochemistry was performed for phospho-tau epitopes pT181, pT217, pS356 and pAS202/pThr205 (AT8). Slides were digitally scanned, and three randomly selected regions of interest were analyzed per case for tau burden and characterization of cell type specificity. Amygdala-restricted cases demonstrated a phospho-tau immunoreactivity patterns similar to those observed in Alzheimer's Disease (AD) and Progressive supranuclear palsy (PSP) cohorts. Morphologic assessment demonstrated prominent astrocytic pathology similar to that of PSP. To assess clinical correlates of this pathology, we constructed a generalized linear model using demographic and clinical variables. We found history of depression was the only variable significantly associated with amygdala-restricted tau pathology. Cases with phospho-tau pathology restricted to only the amygdala demonstrated an atypical distribution pattern compared to known tauopathies. While phosphoepitope profiles largely overlapped with comparison cohorts, morphologic assessment identified prominent astrocytic pathology with PSP-like

features. The significant association with depression suggests potential clinical relevance of localized amygdala tau pathology.

Disclosures: H.R. Williamsen: None. **M.L. Hunter:** None. **M.M. Hefti:** None. **K.L. Fiock:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.06/X8

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

Support: AG075802
AG060477
AG053435
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Rainwater Charitable Foundation
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Title: Early orexinergic neuron loss in Alzheimer's disease is linked to ptau-induced innate immune and lysosomal changes: insights from a human postmortem study

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Abstract: Identifying which neurons degenerate earliest in Alzheimer's disease (AD) is critical for understanding disease pathogenesis and developing disease-modifying strategies. Arousal circuits and linked sleep-wake disruptions are affected in prodromal AD, yet the mechanisms underlying the selective loss of wake neurons remain unclear. Here, we show a significant loss of wake-promoting orexin neurons (Ox^N) from Braak stage (BB) I, accompanied by changes in genes related to innate immunity and early response, as well as microglial, lysosomal, and neuronal integrity proteins. We propose that early ptau accumulation primes Ox neurons for selective vulnerability through immune-mediated mechanisms in prodromal AD. This highlights an opportunity to repurpose Ox-targeting therapies to treat prodromal sleep-wake changes and potentially modify AD progression. We used unbiased stereology on postmortem human brains spanning AD BB0-VI (n=40), free of co-pathology. Hypothalamic sections were immunostained

for OxA and the ptau marker CP13, with Nissl counterstaining. To define Ox-related molecular changes, we performed RNA sequencing in the lateral hypothalamic area (LHA) with glial profile and customized neuropathology panels using Bruker nCounter platform across progressive AD stages (n=55), while GeoMx DSP was used for protein profiling (n=28) of Ox^N in early and late AD. Genes and proteins with $p_{adj}<0.05$ were deemed differentially expressed. Unbiased stereology showed a 43% reduction in Ox^N count at BBI relative to BB0 ($p_{adj}=0.042$), progressing to a 74% reduction by BBV-VI ($p_{adj}=0.0004$). While $ptau^+$ neurons were detectable at BB0, their proportion became significant from BBIII-IV. Earliest transcriptional changes include upregulation of innate immune and lipid-oxidation genes with downregulation of early-response genes. Further, proteomic analysis revealed reactive gliosis, perturbations in lysosomal-UPS and protein-clearance, loss of myelin, synaptic, neuronal and vascular integrity proteins, and axonal injury as the earliest changes in Ox^N in AD. Overall, we identified orexin neurons as the earliest neuronal population to degenerate in AD, beginning at BBI. Early ptau accumulation in LHA devoid of Aβ pathology is linked to immune activation, impaired proteostasis, lysosomal dysfunction, and compromised neuronal integrity. This highlights that Ox^N, a previously underrecognized target, may provide both symptomatic and disease-modifying benefits. We provide mechanistic support for further investigation of available Ox-modulatory drugs as therapeutic targets to mitigate sleep-wake dysregulation in AD and slow disease progression.

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Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.07/X9

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

Support: NIH Grant R01AG070193
NIH Grant K01AG057862
Alzheimer's Association AARFD-19-616386

Title: Pathogenic tau inhibits synaptic plasticity by blocking eIF4B-mediated local protein synthesis

Authors: *G. KAUWE[1], I. WONG[2], K. SCHNEIDER[1], L. YAO[1], K. PAREJA-NAVARRO[3], C. M. KARCH[4], L. GAN[5], T. E. TRACY[1];
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Abstract: Activity-dependent modulation of synaptic strength is critical for encoding memories and it is inhibited in tauopathies including Alzheimer's disease (AD) and Frontotemporal lobar degeneration with tau inclusions (FTLD-tau). Pathogenic tau accumulates in neurons where it obstructs synaptic plasticity. How tau blocks synaptic plasticity leading to memory loss is unclear. Here, we used human iPSC-derived neurons to show that FTLD-tau inhibits plasticity by blocking activity-dependent protein synthesis in dendrites. In the plasticity-associated translatome, we identified a subset of downregulated translated mRNAs in FTLD-tau neurons that encode postsynaptic plasticity regulators. Activity-induced protein synthesis in FTLD-tau neurons was blocked by tau binding to eIF4B which caused eIF4B dissociation from the translation initiation complex and reduced dendritic eIF4B levels. We show in the PS19 tauopathy mouse model that eIF4B protein levels are reduced in the molecular layer of the dentate gyrus. Expression of eIF4B in the hippocampus restores synaptic plasticity and memory performance in PS19 mice. Inhibiting the tau-eIF4B interaction or enhancing eIF4B levels in human FTLD-tau neurons restored local protein synthesis and synaptic plasticity. Together, this suggests that pathogenic tau binding to eIF4B disables the local synthesis of plasticity-related proteins that drive synapse strengthening and memory formation.

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Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.08/X10

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

Support: NIH 2020 K08 NS

Title: Patient-derived brain homogenate as a disease-relevant seeding model for Lewy body dementia

Authors: *S. SMADI[1], R. THANGAVEL[1], K. GUPTA[1], J. RYSTED[2], A. BERTOLLI[1], G. M. ALDRIDGE[1];
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Abstract: Lewy body dementias (LBDs), including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), are characterized by the accumulation of alpha-synuclein (α-syn) protein aggregates deposited in multiple regions of the brain. In both conditions, α-syn aggregates extend beyond the brainstem into the cortex, and patients experience increased risk of delirium and executive dysfunction. Previous work from our group has shown that injecting

synthetic α-syn pre-formed fibrils (PFFs) into the prefrontal cortex of mice led to phospho-syn aggregation in cortical and subcortical areas, as well as mild prefrontal-associated behavioral changes. We have also used viral overexpression of α-syn combined with synthetic PFFs in the ventral tegmental area (VTA) and found evidence of aggregation and depletion of dopaminergic neurons via TH immunofluorescence. However, research from other groups (Sokratian et al. 2024) has shown that synthetic PFFs generate synuclein aggregates that more closely resemble those found in multiple system atrophy (MSA), whose fibrils are more potent at seeding aggregation than LBD. Unlike LBD, MSA pathology affects glial cells rather than neurons and presents with autonomic dysfunction rather than cognitive symptoms. Furthermore, most LBD patients have co-aggregates with at least one other protein pathology, especially phospho-tau. Better animal models are needed to reflect this heterogeneity. We hypothesize that synthetic PFFs may not accurately model LBD, as these MSA-like fibrils target different circuits and cell types, creating a separate phenotype and pathological presence, and that whole-brain homogenate derived from individual patients will induce pathology that better reflects the pattern of circuit vulnerability in these diseases. To test this hypothesis, we used patient-derived brain homogenate from confirmed cases of LBD and MSA and a control donor to assess whether disease-relevant human synuclein aggregates would reproducibly model individual patients' patterns of pathology spread and cognitive symptoms. Mice were split into groups and assigned to one of three different injection sites, chosen due to their projections to the VTA, LC, and cortex, all implicated in symptoms that have differential penetrance in LBD. After recovering from surgery, mice were run on a battery of behavioral tests to screen the phenotype. Mice were then processed to confirm the presence of pathology in the brain. Intriguingly, pilot analysis found that after injecting LBD brain homogenate at Bregma -1.07, evidence of both p-syn and tau aggregates was found in neurites near the hippocampus and cortex.

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Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.09/X11

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

Title: A Comprehensive in vitro Platform for Functional Assessment of Tau-Targeted Small Molecules and PROTACs Drugs

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and leading cause of age-related dementia, marked by senile plaques, neurofibrillary tangles (NFTs), and

neuronal damage. NFTs consist of paired helical filaments (PHFs), which drive neurotoxicity and facilitate tau spread. Tauopathy development remains challenging due to incomplete understanding of tau-mediated damage and lack of well-characterized disease-relevant tau conformations. Here, we report a systematic in vitro platform for assessment of tau binding, aggregation, and degradation.We characterized human Tau-441 preformed fibrils (PFFs) using TEM. Negative staining revealed PHFs with an ~80 nm periodic twist and 10-20 nm width, closely resembling AD patient-derived tau filaments. AD-like straight fibrils were also observed. SPR confirmed that small-molecule ligand T807 binds tau fibrils with higher selectivity and affinity than monomers. Thus, tau PFFs recapitulate key AD-associated pathological features, providing a solid basis for evaluating tau-targeted modulators and degraders.To track intracellular tau conformational changes and aggregation, we developed a sensitive NanoBiT-based biosensor. HEK293 cells expressing LgBiT-Tau441(P301L) and SmBiT-Tau441(P301L) quantify tau aggregation via luminescence. Tau(K18) PFFs induced endogenous tau aggregation dose-dependently, demonstrating a robust high-throughput tool for screening aggregation inhibitors and tau-targeting degraders. This biosensor enables dynamic, quantitative detection of pathological tau aggregation, addressing the demand for phenotypic screening in tau drug discovery.We further established a tau seeding and degradation assay to evaluate PROTAC efficacy. Tau(K18)-EGFP HEK293 cells were incubated with Tau seeds for 24h, followed by PROTAC addition. Soluble-insoluble fractionation western blot showed PROTACs substantially reduced insoluble tau aggregates. Tau Aggregation HTRF assay further confirmed that PROTAC effectively reduced tau aggregates. These assays provide reliable functional approach to quantify therapeutic potency of tau-targeted PROTAC candidates against pathological tau accumulation.In summary, we built an integrated in vitro system covering tau structural characterization, molecular binding profiling, aggregation monitoring, and PROTAC-mediated degradation. This multi-dimensional platform streamlines validation of tau-targeted small molecules and PROTACs. Featuring high sensitivity and throughput, it supports large-scale compound screening, functional validation, and translational research for tauopathy therapeutics.

Disclosures: X. Du: None. **L. Wen:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.10/X12

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

Support: PI22/00938/Instituto de Salud Carlos III
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IN607A2022/07/Xunta de Galicia
Horizon 2020 project PANA - grant number 686009

Ministry of Science and Innovation RTC2019-007373-1
IN607A2026-09/Xunta de Galicia

Title: A THERAGNOSTIC APPROACH FOR TAUOPATHIES FOCUSED ON PHOSPHORYLATED TAU

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Abstract: Background: Currently, there is no effective approach for the early diagnosis and treatment of tauopathies. This study suggests a theragnostic approach based on the importance of phosphorylated tau protein (p-Tau) in the early pathophysiological processes of tauopathy. We have developed a novel theragnostic monoclonal antibody (mAb) to provide both diagnostic and therapeutic effects. Methods/Results: We have developed a p-Tau mAb, which was doped with deferoxamine for radiolabeling with Zirconium-89 (89Zr) for PET imaging, as well as fluorescence dies for immunofluorescence assays. The p-Tau mAb was evaluated in vitro for toxicity by MTT assay, LDH activity, propidium iodide/Annexin V assay, caspase-3, and mitochondrial membrane potential (MMP) assay, in both mouse endothelial cell line (bEnd.3) and cortical primary neurons cell cultures. Importantly, non-toxic effects (up to concentrations of p-Tau mAb greater than 100 ug/mL) were detected. In vivo experiments in the tauopathy model mice (PS19) show that the 89Zr-pTau-mAb and 89Zr-Fragments-pTau-mAb are stable in circulation for up to 10 days, without toxic effects. Moreover, an intraparenchymal treatment strategy was carried out. The PS19 mice were operated to implement osmotic pumps (Alzet 1004) at two different times, at 4 and 7 months, to stimulate the controlled release for one month each of the B6 antibody or the IgG1 control antibody. We demonstrated that B6-treated mice maintained their motor and memory abilities significantly compared with IgG1 treatment. In addition, we observed a significant reduction in p-Tau deposits in the brain. Conclusions: A theragnostic pTau-mAb was developed and recognizes very-early pathology forms of p-Tau by non-invasive techniques, such as PET. In addition, p-Tau mAb has non-toxic effects and mediated cognitive improvement in PS19 preclinical model of Tauopathy.

Disclosures: T. Sobrino: None. **D. Romaus-Sanjurjo:** None. **J. Castillo:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.11/X13

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

Title: Structural remodeling of tau aggregation by small molecules to attenuate tau-induced neurotoxicity

Authors: *A. FRANCO[1], J. ZENG[2], C. LO[3];
[1]Biomed. and Chem. Engin., [3]Biol., [2]Syracuse Univ., Syracuse, NY

Abstract: Tau paired helical filaments (PHFs) and neurofibrillary tangles, composed of fibrillar tau, are defining histopathological hallmarks of Alzheimer's disease (AD) and related tauopathies. Although tau fibrils contribute to neurotoxicity and seed tau propagation, emerging evidence suggests that some fibrillar states may reduce toxicity by sequestering toxic oligomeric intermediates. This duality highlights the therapeutic potential of structurally remodeling tau assemblies toward less toxic forms by a drug repurposing process. Here, we developed an integrated computational and experimental pipeline to identify structural modulators of tau aggregation through a drug repurposing strategy incorporating small molecules. Using a structure-based approach based on the cryo-EM structure of AD-derived tau PHFs (PDB: 5O3L) we performed virtual screening of the NIH Clinical Collection which revealed preferential binding to two structural hotspots: the C-shaped pocket and the inter-protofilament cleft. Eight candidate compounds significantly altered tau aggregation kinetics and produced distinct effects on neuronal viability. Epirubicin, doxycycline, oxytetracycline, and danazol inhibited aggregation and rescued tau-induced cytotoxicity in SH-SY5Y cells. In contrast, risperidone and tibolone promoted aggregation yet remained protective, while dexamethasone and betamethasone exacerbated toxicity, underscoring the complex relationship between aggregation and neurotoxicity. Molecular dynamics simulations revealed compound-specific remodeling mechanisms, including β-sheet disruption, altered protofilament packing, and changes in fibril surface properties, quantified through hydrogen bonding, solvent-accessible surface area, and structural dynamics. Clustering analysis defined four functional classes of tau modulators: direct inhibitors, oligomer-sequestering agents, neuroprotective remodelers, and seeding-enhancing compounds. Several candidates also showed predicted blood-brain barrier permeability, supporting translational potential. Overall, this work shows that small molecules reshape tau aggregation through diverse structural mechanisms, establishing a structure-guided framework for discovering brain-penetrant therapeutics and linking fibril remodeling to functional outcomes in tauopathies.

Disclosures: A. Franco: None. **J. Zeng:** None. **C. Lo:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.12/X14

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

Support: Coulter Translational Fund

Title: Investigating the role of tau pre-formed fibrils in exacerbating alpha synuclein-induced neurotoxicity

Authors: *J. N. HUNT[1], D. DHAVALE[3], P. T. KOTZBAUER[3], S. KORTAGERE[2]; [1]Microbiology & Immunol., [2]Microbiology and Immunol., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting over 10 million people worldwide and represents a major public health burden due to its increasing prevalence and lack of disease-modifying therapies available. Although aggregation of α-synuclein into Lewy bodies is a defining feature of PD, growing evidence indicates that mixed proteinopathies are common, with hyperphosphorylated tau frequently co-localizing with α-synuclein aggregates. These overlapping protein accumulations are associated with accelerated cognitive decline and worse clinical outcomes, yet the mechanistic role of tau in α-syn-mediated toxicity remains poorly understood. Elucidating this interaction is therefore critical for improving our understanding of disease progression and identifying new therapeutic targets. Here, we propose that tau pre-formed fibrils (PFFs) potentiate α-syn PFF-induced glutamatergic dysregulation and excitotoxic signaling, resulting in enhanced neurotoxicity compared to either protein alone. Specifically, we will test whether combined α-syn and tau pathology leads to greater excitotoxic signaling, as reflected by increased calcium influx and elevated glutamate levels, relative to single-protein conditions. We hypothesize that tau PFFs act synergistically with α-syn PFFs to exacerbate neuronal dysfunction through dysregulation of glutamatergic signaling pathways. Overall, these findings will provide mechanistic insight into neurodegeneration in mixed proteinopathies and to identify pathways that may be targeted for therapeutic intervention in PD and related neurodegenerative disorders.

Disclosures: J.N. Hunt: None. **D. Dhavale:** None. **P.T. Kotzbauer:** None. **S. Kortagere:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.13/X15

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

Support: NIH RO1/5R01NS136448-03
CurePSP/693-2024-03-Urso
University of Iowa, Graduate College

Title: Tau Phosphorylation State Determines Astrocytic Fate: Uptake, Degradation, and Toxicity of Monomeric Tau

Authors: *N. FIROUZSHAHI[1], M. R. SHIN[1], M. WEIS[2], B. DOLATYAR[3], M. M. HEFTI[1]; [2]Neurosci. and Pharmacol., [1]Univ. of Iowa, Iowa City, IA; [3]Univ. of Iowa, IOWA CITY, IA

Abstract: Background: Tauopathies are a class of neurodegenerative diseases defined by abnormal tau aggregation. Importantly, primary tauopathies, including progressive supranuclear palsy (PSP), are characterized by prominent astrocytic tau pathology. Astrocytes internalize extracellular tau released from neurons, positioning them as active participants in tau propagation. Prior studies have primarily focused on astrocytic processing of fibrillar and oligomeric tau, with little attention given to tau monomers. This is a critical gap because monomeric tau precedes aggregated tau species and is encountered by astrocytes early in disease progression, when disease-associated phosphorylation patterns are starting to emerge. Therefore, how astrocytes process monomeric tau, particularly in the context of phosphorylation, remains largely unexplored.
Methods: Human induced pluripotent stem cell (iPSC)-derived astrocytes were used to determine how serine/threonine (S/T) and tyrosine (Y) phosphorylation affect uptake and degradation of recombinant monomeric 1N4R tau. PSP tissue confirmed findings in a disease-relevant context. Tau uptake, clearance, and astrocyte cytotoxicity were assessed using live-cell imaging, immunocytochemistry, immunoblotting, and immunofluorescence.
Results: S/T phosphorylation significantly impaired astrocytic uptake of monomeric tau through dynamin-dependent endocytosis, whereas Y phosphorylation had no effect. This reduction was astrocyte-specific and was not observed in iPSC-derived neurons. Despite reduced uptake, S/T-phosphorylated tau produced greater cytotoxicity. Internalized tau trafficked to lysosomes in vitro which was further confirmed in PSP tissue. Phosphorylation-specific immunostaining of PSP tissue detected S/T-phosphorylated but not Y-phosphorylated tau in astrocytes. Tau degradation was driven primarily by autophagy, with proteasomal degradation contributing exclusively to unphosphorylated tau clearance.
Conclusion: These findings demonstrate that tau phosphorylation state differentially regulates astrocytic uptake, clearance, and cytotoxicity. S/T phosphorylation, elevated in Alzheimer's disease, which lacks significant glial tau pathology, impairs astrocyte-mediated tau uptake while increasing cellular toxicity. Y phosphorylation, however, leaves these processes intact. These results identify phosphorylation-dependent astrocytic processing of monomeric tau as a potential driver of cell-type specific pathology, highlighting the potential for astrocyte-directed treatments aimed at limiting tau propagation in early stages of tauopathies.

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Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR308.14/X16

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

Support: CIHR Grant PJT - 173540

Title: Evaluation of the novel 4R tau PET tracer [^{18}F]OXD-2314 in progressive supranuclear palsy: a preliminary study

Authors: *C. CHOW[1,2], L. NARCISO[2], J. S. RABIN[3,1], I. BOILEAU[2,1], J. BELOBRAJDIC[4], K. L. DESMOND[5], N. VASDEV[2], A. P. STRAFELLA[2,1,6];
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Abstract: Progressive supranuclear palsy (PSP) is the most common atypical parkinsonism and is characterized by the accumulation of 4-repeat (4R) tau aggregates. Accurate diagnosis remains challenging due to overlapping clinical features with other parkinsonian disorders and the lack of validated in vivo biomarkers. Although positron emission tomography (PET) imaging enables in vivo imaging of tau pathology, many existing radiotracers demonstrate variable sensitivity to 4R tau and may exhibit off-target binding, limiting their utility in PSP. This preliminary study aims to examine the use of the novel 4R tau PET radiotracer, [^{18}F]OXD-2314, in PSP subjects and age- and sex-matched healthy controls. 6 individuals with clinically diagnosed PSP (65.67 ± 9.33 years; 3 female; disease duration: 29.67 ± 20.57 months; PSPRS: 27.67 ± 9.85; phenotypes: 2 PSP-RS, 2 PSP-P, 1 PSP-SL, 1 PSP-C) and 6 healthy controls (59.50 ± 11.36 years, 3 female) underwent PET imaging on a GE Discovery PET/CT system. Scans were analyzed using PMODv4.2, which included motion correction and co-registration to the participant's T1-weighted MRI scan. Standardized uptake value ratio (SUVR) was calculated using a 60-90 min post-injection time window with cerebellar gray matter as the reference region. Regions-of-interest (ROI) were extracted using predefined atlases including the substantia nigra (SN), globus pallidus (GP), subthalamic nucleus (STN), dentate nucleus (DN), medial prefrontal cortex (mPFC), and dorsolateral prefrontal cortex (dlPFC). Between-group differences were assessed using independent-samples *t*-tests with Welch's correction for unequal variances. PSP participants demonstrated significantly greater [^{18}F]OXD-2314 uptake in the GP ($t(8.54) = 2.51$, $p = 0.035$, Cohen's $d = 1.45$) and STN ($t(9.54) = 3.26$, $p = 0.009$, $d = 1.88$), with elevated uptake in the SN ($t(9.66) = 2.14$, $p = 0.058$, $d = 1.23$) and DN ($t(9.03) = 2.01$, $p = 0.076$, $d = 1.16$) approaching significance. No significant differences were observed in the mPFC or dlPFC. These preliminary findings demonstrate increased [^{18}F]OXD-2314 uptake in PSP, with the strongest effects observed in the GP and STN. The regional patterns are consistent with the prominent basal ganglia involvement observed in PSP and supports further evaluation of [^{18}F]OXD-2314 as a potential biomarker for in vivo detection of 4R tau pathology. Larger cohorts are needed to validate these findings and determine relationships between tracer uptake and clinical phenotype.

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Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.15/X17

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

Support: University of Hartford Dean's Research and Teaching Funds

Title: ApoE and the astrocytic response to physiological levels of inactive monomeric alpha-synuclein

Authors: A. J. GOUVAN[1], A. BRAHIMI[2], ***A. O. KOOB**[2];
[1]Psychology Department, Neurosci. Program, [2]Biol. Department, Neurosci. Program, Univ. of Hartford, West Hartford, CT

Abstract: Inheritance of the APOE4 allele results in an increased risk for neurodegenerative disease, and has traditionally been associated with Alzheimer's disease. Recent evidence indicates that APOE4 is also a risk factor for synucleinopathies such as dementia with Lewy bodies and Parkinson's disease. Likewise, synuclein pathology is observed concurrently in ~50% of cases of Alzheimer's disease diagnoses. Astrocyte-derived apolipoprotein E (apoE) accounts for ~75-80% of secreted apoE in the brain. In order to better understand the relationship of apoE, astrocytes and synucleins, APOE3+/+ and APOE4+/+ iPSC-derived astrocytes were challenged with physiological levels of inactive monomeric alpha-synuclein (100 nM and 500 nM) to mimic healthy brain conditions. LDH assays indicated that both APOE3 and APOE4 astrocytes did not have reduced cell viability after 24 hours of treatment. Live cell imaging of intracellular calcium (Ca2+) levels for 5 seconds prior and 1 min after treatment revealed that both APOE3 and APOE4 astrocytes responded to 5 μM glutamate as a positive control when compared to Tris-HCL as a negative control. However, only APOE3 astrocytes responded to alpha-synuclein at 100 nM, while both responded to 500 nM when compared to controls. Endolysosomal processing was analyzed through colocalization of CD63 and LAMP1 immunocytochemical markers after 24 hours of alpha-synuclein treatment. APOE3 astrocytes underwent healthy autolysosomal formation and degradation, as indicated by less LAMP1 colocalizing with CD63, while APOE4 astrocytes did not proceed to autolysosomal formation and developed perinuclear endolysosomal accumulation in all conditions. The results here indicate that the astrocytic response to inactive monomeric alpha-synuclein at physiological levels results in healthy lysosomal processing and calcium signaling in APOE3+/+ cells in order to degrade and remove excess extracellular alpha-synuclein, whereas APOE4+/+ astrocytes did not respond through signaling pathways and the endolysosomal system was disrupted. Further investigation into these possible differences with isogenic cells lines could shed light on biochemical and physiological pathways disrupted in APOE4 astrocytes that result in increased disease risk in synucleinopathies.

Disclosures: A.J. Gouvan: None. **A. Brahimi:** None. **A.O. Koob:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.16/X18

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

Support: National Institutes of Health [1R01AG084552-01A1]

Title: Characterizing the effects of mutations in ATPases in tauopathy

Authors: *A. SCIOCCHETTI[1], R. ECK[2], R. L. KOW[3];
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Abstract: Neurodegenerative diseases such as Alzheimer's Disease (AD) and Frontotemporal dementia affect over 7 million people in the United States alone, and yet the mechanism of these diseases remains unclear. Current treatments of AD primarily focus on amyloid beta pathology, but no treatment has been clinically effective in preventing progression of the disease. Tau is a protein that functions in microtubule stability but forms aggregates that kill neurons when hyperphosphorylated in the diseased state. Our lab investigates the molecular mechanisms of tau toxicity using a C. elegans model expressing human tau in all of its neurons. C. elegans are nematodes, a type of worm commonly used in neuroscience research due to fast generation time, well-understood genome, and transparency. RNA sequencing of one of our C. elegans models of tau toxicity revealed upregulation of catp-2, which encodes a sodium-potassium ATPase transporter important for cation transport, leading to our interest in investigating the gene in our tau models. We have shown mutations in catp-2 to have modest suppression of tau-induced toxicity in our C. elegans models, so we further investigated genes that may interact with the ATPase to better understand the contribution to disease. One of these genes is nkb-3, which plays a role in the same pathway as catp-2 and may even participate in the formation of the same ATPase complex. In addition, it is another gene expressed to a greater degree in our C. elegans model of tau toxicity at the larval stage. Research suggests DNA damage may lead to a stress response in which proteostatic and metabolic pathways become upregulated. The upregulation of genes such as catp-2 and other ion pumps may alter cell signaling dynamics and the localization of receptors such as the acetylcholine receptor (AChR) that may lead to abnormal neuronal firing and death. By studying genes involved in ion transport and cell signaling, we have greater insight into potential mechanisms of tau toxicity.

Disclosures: A. Sciocchetti: A. Employment/Salary (full or part-time):; Seattle Institute for Biomedical and Clinical Research. **R. Eck:** A. Employment/Salary (full or part-time):; University of Washington. **R.L. Kow:** A. Employment/Salary (full or part-time):; Veterans Affairs Puget Sound Health Care System.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.17/X19

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

Support: NIH Grant [1R01AG084552-01A1]

Title: The effect of hel-1 mutations on tau-associated phenotypes in C. elegans models

Authors: *K. J. NELSON[1,2], A. BEALE[1,2], A. SCIOCCHETTI[3,2], B. C. KRAEMER[4,2,5], R. L. KOW[2,6];
[1]Seattle Inst. for Biomed. and Clin. Res. (SIBCR), Seattle, WA; [2]Geriatrics Res. Educ. and Clin. Ctr., Veterans Affairs Puget Sound Hlth. Care Syst., Seattle, WA; [3]Seattle Inst. for Biomed. and Clin. Res., Seattle, WA; [4]Div. of Gerontology and Geriatric Med., Univ. of Washington Sch. of Med., Seattle, WA; [5]Dept. of Lab. Med. and Pathology, [6]Div. of Gerontology and Geriatric Med., Univ. of Washington, Seattle, WA

Abstract: Tau aggregation is a hallmark of many tauopathies and contributes to neuronal dysfunction. The exact mechanisms of tau toxicity are not completely understood. To explore these mechanisms, we used forward mutagenesis screening to identify candidate genes and molecular pathways for further investigation. Through this screen we identified a mutation in *hel-1* that affects the tau-associated phenotypes in a *C. elegans* strain expressing human tau. The first mutation studied, *hel-1(A225G)*, was discovered through forward mutagenesis screening of a tau expressing strain. The second mutation studied, *gk191,* deletes *hel-1* and is an obligatory heterozygote because a full knockout is lethal. The *hel-1* gene encodes a conserved RNA helicase with potential roles in RNA processing; we hypothesized that it may alter tau expression or the associated phenotypes in our *C. elegans* tau models. We assessed the *hel-1* mutants in a tau background for changes in behavioral phenotype, tau protein expression, and mRNA expression of various targets. *C. elegans* strains with either mutation displayed significant improvement in swimming behavior compared to the tau expressing control strain, indicating a robust suppression of tau-induced motor impairment. Preliminary results from our lab show that *hel-1(A225G)* reduces total tau protein. These results suggest an important role for *hel-1* in modulating tau-associated pathology in *C. elegans* models of tau toxicity, likely through the regulation of tau expression at the RNA or protein level. The suppression of tau-induced motor deficits in the *hel-1* mutants combined with the reduction in tau protein expression supports a model in which *hel-1* activity influences tau abundance and/or stability. Identifying conserved regulators of tau expression has important implications for understanding the progression of tauopathies and may point to novel therapeutic targets in human disease.

Disclosures: K.J. Nelson: None. **A. Beale:** None. **A. Sciocchetti:** None. **B.C. Kraemer:** None. **R.L. Kow:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.18/X20

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

Support: West Michigan Neuro-degenerative Diseases Program Pilot Award (MiP.017)

Title: Cryo-EM structures of α-synuclein filaments from Multiple System Atrophy and Parkinson's disease variant with PET tracer ACI-12589

Authors: *K. N. ERNST;
Structural Biol., Van Andel Inst., Grand Rapids, MI

Abstract: Accumulation of misfolded α-synuclein is a defining pathological feature of synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Recent evidence indicates that disease-specific α-synuclein filament conformations, or folds, contribute to the distinct clinical and pathological characteristics of these disorders. Positron emission tomography (PET) imaging has emerged as a promising tool for detecting pathological α-synuclein in vivo. Among recent developments, the PET tracer [^{18}F]ACI-12589 has shown stronger affinity for MSA from other synucleinopathies. The binding mechanism of PET tracers to α-synuclein filaments from MSA or PD variants have not yet been determined. Here we show the cryo-EM structures of ACI-12589 binding to type I and type II MSA α-synuclein filaments at resolution of 2.7 Å and 2.6 Å, respectively. The tracer occupies a conserved binding cleft at the C-terminus of protofilament A, adopting a diagonal geometry and stabilized by π-π aromatic stacking interactions with C-terminal residues. To investigate the structural determinants underlying tracer selectivity, we further determined cryo-EM structures of ACI-12589 incubated with α-synuclein filaments adopting singlet and doublet Lewy fold derived from PD brains at 3.0Å and 3.3 Å resolution, including PD variants with SNCA H50Q and G51D mutations. Comparative analysis reveals that ACI-12589 binds to MSA filaments and dimerised Lewy fold assemblies, but not to singlet Lewy fold conformation, providing a molecular explanation for the selective recognition of distinct α-synuclein filament folds. These findings support the clinical utility of [^{18}F]ACI-12589 for disease stratification and longitudinal monitoring, and highlight fold-specific cavities on α-synuclein as actionable sites for next-generation imaging agents and therapeutics.

Disclosures: K.N. Ernst: None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.19/X21

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

Support: National Institutes of Health/National Institute of Neurological Disorders & Stroke (NIH/NINDS) [RF1-NS113548-01A1 to OC-F]
National Institutes of Health/National Institute on Aging (NIH/NIA) [R01 AG057522 and RF1 AG077695 to OC-F]

Title: Cell-Type-Specific Molecular Signatures of Parkinson's Disease and Dementia with Lewy Bodies in African-Ancestry Donors Revealed by Single-Cell Long-Read Sequencing

Authors: *D. AXON[1], D. HODGSON[2], E. SHWAB[2], O. CHIBA-FALEK[2];
[1]Duke Univ., Durham, NC; [2]Duke Med., Durham, NC

Abstract: Due to insufficient representation of non-European populations in genetic research, we lack a robust understanding of the ancestry-specific pathophysiology driving neurodegenerative diseases like Parkinson's Disease (PD) and dementia with Lewy Bodies (DLB). PD and DLB demonstrate highly variable clinical phenotypes that can be influenced by alpha-synuclein pathology, co-pathology, genetics, age, and environmental factors. In order to unravel the complex molecular changes that underlie these diseases, we employed an unbiased single-cell long-read sequencing approach to characterize gene-level expression changes and pathway enrichment in specific neuronal and glial populations. Nuclei were isolated using frozen human temporal cortex tissue samples from donors clinically diagnosed with DLB (n = 10), PD or PDD (n = 9), as well as normal control donors (n = 12). The tissue donors all had African ancestry. Once the samples had been sequenced, expression data were integrated and annotated according to major brain cell types and cell subtypes by label transfer. Downstream analyses independently comparing PD and DLB to healthy controls revealed 2,951 differentially expressed genes (DEGs) in PD and 998 DEGs in DLB. PD showed the strongest molecular alterations in inhibitory neuron subtypes, with widespread changes in synaptic function, cellular transport, autophagy, stress responses, and cytoskeletal organization, while DLB changes were concentrated in excitatory neurons and primarily affected synaptic signaling, neuronal excitability, and post-transcriptional regulation. Many PD-associated DEGs overlapped established PD GWAS risk genes, including MAPT and VPS13C, suggesting that the observed transcriptional changes are closely linked to known genetic mechanisms of disease. These findings provide important insight into ancestry-specific molecular features of synucleinopathies and demonstrate the value of long-read single-cell sequencing for identifying cell-type-specific disease mechanisms and potential therapeutic targets in underrepresented populations.

Disclosures: D. Axon: None. **O. Chiba-Falek:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.20/X22

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

Support: NIH NS134833

Title: Morphologic analysis of the impact of alpha-synuclein on locus coeruleus neurons in mouse models and human disease

Authors: *G. H. SCHOENING[1], G. M. ALDRIDGE[1], K. GUPTA[2];
[1]Neurol., Univ. of Iowa, Iowa City, IA; [2]Systems Neurophysiol., Dept. of Neurology, Univ. of Iowa, Iowa city, IA

Abstract: The locus coeruleus (LC) is a brainstem noradrenergic nucleus that regulates arousal, attention, and sleep-wake state and is among the earliest regions to accumulate alpha-synuclein (α-syn) pathology in Parkinson's disease dementia and dementia with Lewy bodies. Although LC pathology is an early feature of synucleinopathies, the relationship between α-syn accumulation and single-neuron structural changes in LC noradrenergic cells remains incompletely characterized. To examine LC vulnerability in experimental α-syn models, mice received viral overexpression of human α-syn, α-syn pre-formed fibril injection, combined overexpression and fibril injection, or saline injection. LC tissue was immunostained for phosphorylated α-synuclein (p-syn), α-syn, tyrosine hydroxylase (TH), and DAPI, then imaged using confocal microscopy. TH-positive LC neurons were classified as p-syn-positive or TH-only control neurons based on immunofluorescent labeling. Regions of interest were then provided in a single channel to ensure morphologic tracing could be performed blinded to pathology status and experimental conditions. We performed single-cell morphologic analysis of LC neurons by tracing their dendritic processes along with soma and nucleus morphology and size. Sholl analysis was used to quantify dendritic complexity, including process distribution and branching relative to the soma, comparing p-syn positive versus negative neurons within each animal. In parallel, p-syn burden in TH-positive LC neurons and stereological analysis was quantified to estimate total TH cell number between injection groups. We hypothesized that LC neurons containing p-syn pathology would show altered cellular morphology compared with non-p-syn neurons within the same animals, as well as saline-injected controls. Interestingly, we found a trend towards both cell-autonomous and cell-non-autonomous impacts of p-syn. This work provides an unbiased, quantitative framework for linking α-synuclein pathology to structural vulnerability of LC noradrenergic neurons in mouse models of synucleinopathy that can be directly compared with morphology of human neurons. Future work will directly compare morphology between different mouse models human autopsy tissue.

Disclosures: G.H. Schoening: None. **G.M. Aldridge:** None. **K. Gupta:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.21/X23

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

Title: Raman Spectroscopic Profiling of Disease Specific Biochemical Signatures in Parkinsons Disease and Alzheimers Disease Brain Microenvironments

Authors: *A. O. OMIRUDE[1], A. O. YUSUF[3], M. D. ATOLAGBE[4], S. M. EZE[5], K. B. RAJI[2]; [1]Human Anat., Ahmadu Bello Univ. Fac. of Med., Middlesbrough, United Kingdom; [2]Ahmadu Bello Univ. Fac. of Med., Zaria, Nigeria; [3]Human Anat., Confluence Univ. of Sci. and Technol., Lokoja, Nigeria; [4]Chem., Teesside Univ., Middlesbrough, United Kingdom; [5]Human Anat., AL-HIKAMH UNIVERSITY, Ilorin, Nigeria

Abstract: Objective We aimed to investigate biochemical differences in Parkinson's disease and Alzheimer'sdisease brain tissue using label-free Raman spectroscopy, focusing on neurons, blood vessels,and surrounding neuropil.**Background**Parkinson's disease and Alzheimer's disease are progressive neurodegenerative disorderscharacterised by abnormal protein accumulation, lipid alterations, and vascular dysfunction.Although they are classically defined by different pathological hallmarks, increasing evidencesuggests shared molecular changes. A key challenge is capturing these biochemical alterationsdirectly within intact brain tissue. Raman spectroscopy provides a label-free method to probemolecular composition in situ without the need for staining or markers.**Methods**Formalin-fixed paraffin-embedded post mortem brain tissue microarrays from Parkinson'sdisease, Alzheimer's disease, and non-neurodegenerative controls were analysed. Afterdeparaffinisation, samples were examined using Raman microscopy with a 785 nm laser.Spectra were collected from neuronal, vascular, and neuropil regions. Approximately 90spectra per group were acquired. Data were processed using baseline correction andnormalisation, followed by principal component analysis to identify biochemical patterns.**Results**Clear biochemical differences were observed between neurodegenerative and control tissues.Neuronal spectra from both Parkinson's disease and Alzheimer's disease showed similaroverall profiles but differed from controls, particularly within the 1000 - 1700 cm^{-1} fingerprintregion. Blood vessel regions showed greater spectral variability in both disease groups,suggesting altered vascular biochemistry. Principal component analysis demonstratedseparation between disease and control samples, driven largely by increased protein- and lipid-associated signals in both neuronal and vascular compartments.**Conclusions**Raman spectroscopy detects distinct biochemical alterations across multiple brain regions inParkinson's disease and Alzheimer's disease. Shared changes in protein and lipid compositionsuggest overlapping molecular mechanisms in neurodegeneration. This label-free approachprovides a promising tool for studying disease-associated biochemical signatures and maysupport future biomarker development in neurodegenerative disorders.

Disclosures: A.O. Omirude: None. **A.O. Yusuf:** None. **M.D. Atolagbe:** None. **S.M. Eze:** None. **K.B. Raji:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.22/X24

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

Support: Syracuse University Start-up grant

Title: BBB-penetrating acidic nanoparticles restore lysosomal acidification and reduce α-Synuclein pathology in familial Parkinson's disease

Authors: *J. ZENG, Y. LIU, X. CHEN, C. LO;
Syracuse Univ., Syracuse, NY

Abstract: Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by α-synuclein (αSyn) aggregation, lysosomal dysfunction, and progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to motor impairment. A key pathological feature of PD is lysosomal deacidification, which reduces hydrolase activity, impairs autophagic clearance, and promotes the accumulation of toxic αSyn species. Restoring lysosomal acidification therefore represents a promising therapeutic strategy, but effective delivery to the brain remains a major challenge. To address this, we developed blood-brain barrier-penetrating acidic nanoparticles (BBB-AcNPs) to restore lysosomal pH. In SH-SY5Y cells overexpressing A30P αSyn, pathological αSyn induced lysosomal alkalization, impaired autophagic flux, mitochondrial dysfunction, and cytotoxicity. BBB-AcNP treatment restored lysosomal acidification, enhanced autophagic flux and mitophagy, improved mitochondrial function, and protected against αSyn-induced cell death. We then evaluated BBB-AcNPs in A30P αSyn transgenic mouse models of familial PD. In vivo, BBB-AcNP treatment enhanced αSyn clearance, reduced dopaminergic neuron loss, and improved motor performance. Together, these findings identify lysosomal acidification dysfunction as a central pathogenic mechanism in familial synucleinopathy and support BBB-AcNP-mediated lysosomal re-acidification as a potential therapeutic strategy for PD and related proteinopathies.

Disclosures: J. Zeng: None. **Y. Liu:** None. **X. Chen:** None. **C. Lo:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.23/X25

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

Support: 1R01AG091184
INI
STEAD SCHOLARS

Title: Exploring the spread of concomitant tau and alpha synuclein pathology through serotonergic, cholinergic, and catecholaminergic neural circuits in mixed dementias.

Authors: Y. LIU, R. THANGAVEL, S. PIERSON, *G. M. ALDRIDGE;
Univ. of Iowa, Iowa City, IA

Abstract: Neurodegenerative dementias, including Alzheimer's, Lewy body dementia, and frontotemporal dementia effect an estimated 57 million individuals worldwide and lead to devastating personal and financial costs. Recent evidence suggests that dementias occur on a spectrum, with aggregation of pathological proteins including amyloid beta plaques, neurofibrillary tangles, TDP-43 inclusions and phosphorylated alpha synuclein-containing Lewy bodies frequently co-occurring. Additionally, these proteins are known to interact synergistically, with phosphorylated tau (pTau) and alpha synuclein (pSyn) co-aggregating, leading to prion-like propagation and spread through connected neural circuits. Currently, the impact of co-pathology on the spread of neurodegenerative disease-related proteins through implicated neuromodulatory systems is unknown. We assess pTau and pSyn pathology in limbic, neocortical, subcortical, brainstem, and cerebellar brain regions. Using strategic triple immunofluorescence, we evaluate overlap of pSyn and pTau with serotonergic, cholinergic, and catecholaminergic markers. Serotonin, acetylcholine, dopamine and norepinephrine are responsible for regulating cognition, mood, arousal, sleep and autonomic functions. These neural circuits are known to be perturbed in neurodegenerative dementias, with respective nuclei, including the dorsal raphe, nucleus basalis of Meynert, substantia nigra, and locus coeruleus being well-characterized areas of pathological protein deposition. Through post-mortem analysis of 30 consecutive autopsy cases, we found differential patterns of limbic-predominant and brainstem-predominant pSyn and concomitant pTau pathology. We also found a striking decrease of fluorescent intensity of cholinergic nuclei compared to controls, indicating selective vulnerability in mixed dementia. pSyn overlap with catecholaminergic neurons in the brainstem was also observed. We compared these distinct patterns of spread with cutaneous pSyn deposition in the peripheral skin at sites used in clinical diagnosis. We contrast these findings with clinical onset of motor, cognitive, sleep and autonomic symptoms to evaluate the impact of pSyn spread through compromised neurocircuitry in mixed dementia cases. Improving our understanding of the relationship between clinically available biomarkers and drug targets of first-line medications using postmortem tissue analysis provides an important step towards understanding the origin of pathological protein aggregation and subtypes, opening new pathways of inquiry for treatment targets.

Disclosures: Y. Liu: None. **R. Thangavel:** None. **S. Pierson:** None. **G.M. Aldridge:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.24/X26

Topic:

Support: NIH Grant 5R01AG091184-02

Title: Changes in astrocyte morphology in response to phosphorylated alpha-synuclein in the human anterior cingulate cortex

Authors: *C. R. PANASUK[1], Y. LIU[1], R. THANGAVEL[1], M. HUNTER[1], S. PIERSON[1], K. FIOCK[2], M. M. HEFTI[1], G. M. ALDRIDGE[3];
[2]Pathology, [3]Neurol., [1]Univ. of Iowa, Iowa City, IA

Abstract: Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disease caused by the buildup of alpha-synuclein (a-syn), and pathological phosphorylated a-syn (p-syn)aggregates throughout the brain. The anterior cingulate cortex (ACC) is particularly vulnerable to p-syn pathology and plays a critical role in attention, executive function, and decision-making, functions that are commonly impaired in DLB. Because astrocytes regulate synaptic activity and metabolic support, pathological astrocytic remodeling may contribute to neuronal dysfunction in vulnerable cortical regions. Studies have shown that astrocytes can display a reactive state in response to a-syn oligomers. However, astrocyte activation in response to synuclein pathology may vary by brain region. Given the importance of the ACC in cognition and its vulnerability to synuclein pathology,characterizing astrocyte activation in this region may give an insight to mechanisms underlying cognitive dysfunction in DLB. Previous work has shown that astrocytes become activated in response to synuclein pathology in the olfactory bulb (Flores-Cuadrado 2021)and the hypothalamus (Thannickal 2007). However, most studies measuring astrocyte activation only use GFAP levels as an outcome measure and do not examine morphological changes of astrocytes, which may be more representative of functional changes. We hypothesized that increased p-syn levels in the ACC will lead to decreased Sholl scores representative of decreased astrocytic process complexity. To evaluate the effect of synuclein on astrocytes in the ACC, we collected sections of ACC from neurodegenerative disease donors and control autopsies. We analyzed postmortem brain tissue from individuals and measured p-syn load and astrocyte morphology using immunofluorescence staining of PS129 and GFAP respectively. Using this dual immunostaining, we are able to study pathology burden, astrocyte morphology, and possible colocalization. Initial analysis across multiple cases demonstrates extensive p-syn pathology in ACC in DLB cases, with complex patterns of astrocyte staining that vary by individual. Understanding the relationship between astrocyte morphology and p-synburden in the ACC may improve our understanding of the pathological processes associated with cognitive impairment in DLB and inform future therapeutic strategies.

Disclosures: C.R. Panasuk: None. **Y. Liu:** None. **R. Thangavel:** None. **M. Hunter:** None. **S. Pierson:** None. **K. Fiock:** None. **M.M. Hefti:** None. **G.M. Aldridge:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.25/X27

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

Support: NS130256
AG065925

Title: Activity-dependent Release of Human Alpha-Synuclein from Drosophila Neuromuscular Junction

Authors: P. BARAL[1], *D. LEE[2];
[1]Biol. Sci., [2]Ohio Univ., Athens, OH

Abstract: Alpha-Synuclein (αSyn) is an abundant synaptic protein which undergoes misfolding and aggregation into β-sheet-rich amyloid fibrils under pathological conditions. These amyloid fibrils and their oligomeric intermediates are toxic to neurons and glia, which is central to a group of disorders known as synucleinopathies including Parkinson's disease (PD) and Lewy body dementia (LBD). An intriguing concept of prion-like propagation of αSyn has emerged, suggesting the spread of pathogenic αSyn between neuroanatomically connected regions to seed further pathology. Neuronal activity seems to play a critical role in modulating αSyn release and propagation, however the underlying mechanism remains unclear.In this study, we investigated the release of αSyn induced by neuronal depolarization utilizing *Drosophila* larval neuromuscular junction (NMJ). Optogenetic technique was used to stimulate neurons that co-express three different αSyn point mutations (A53T, A30P and E46K) in addition to channel rhodopsin (ChR2). Released αSyn were collected from hemolymph of the third instar larva and quantified by ELISA to compare the levels of released αSyn. Moreover, the influence of synaptic transmission on activity-dependent αSyn release were also assessed. ELISA results showed that αSyn release was enhanced by ChR2-mediated neuronal excitability of glutamatergic motor neurons. There was a higher activity-dependent release of αSyn in mutants A53T and E46K compared to wildtype αSyn but no significant difference in A30P mutant. To test whether αSyn release is due to the point mutations themselves or due to differences in their expression levels, the amount of whole body αSyn was determined which showed that there was no significant difference in the whole body αSyn expression levels between A53T and E46K compared to αSyn (WT), demonstrating that mutant αSyn shows higher release propensity. We also observed that temporal regulation using temperature sensitive Shibire (shi) protein blocked synaptic transmission thereby preventing αSyn release, indicating that activity-dependent αSyn release is primarily driven by a synaptic transmission-dependent mechanism. Currently, we are studying the role of phosphorylation in activity-dependent release of αSyn (e.g., pS129) and characterizing biochemical nature of released αSyn by neuronal hyperexcitability.Our findings provide important insight into the release mechanism of αSyn, a key protein involved in PD and LBD. Together, this study strengthens the understanding of αSyn cell-to-cell propagation mechanisms and provides valuable insight for future PD and LBD research and therapeutic development.

Disclosures: P. Baral: None. **D. Lee:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.26/X28

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

Support: ALSFindingACure
Hop on a Cure

Title: Assess the overlap of TDP-43 pathology between amyotrophic lateral sclerosis and hereditary spastic paraplegia using human organoid and assembloid models

Authors: *M. LINDNER-JACKSON[1], S. RAMAKRISHNAN[3], D. A. BOSCO[4], L. QIANG[2]; [2]Neurobio. and Anat., [1]Drexel Univ. Col. of Med., Philadelphia, PA; [3]Drexel Univ. Col. of medicine, Philadelphia, PA; [4]Neurol., Univ. of Massachusetts, Worcester, MA

Abstract: Age-related neurodegenerative disorders increasingly share molecular pathways despite distinct genetic causes and clinical syndromes. One prominent example is pathology involving TAR DNA-binding protein 43 (TDP-43), an RNA-binding protein whose nuclear depletion and cytoplasmic accumulation occur not only in amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration, but also in age-associated dementias such as limbic-predominant age-related TDP-43 encephalopathy (LATE) and mixed Alzheimer's disease-related dementias. TDP-43 is therefore emerging as a key determinant of neuronal vulnerability, RNA dysregulation, and network dysfunction in the aging brain. However, human model systems capable of explaining how distinct genetic insults converge on TDP-43 dysfunction remain limited. Our lab addresses this gap by investigating two motor neuron disorders traditionally studied separately: C9ORF72-associated ALS and Hereditary Spastic Paraplegia type 4 (SPG4), caused by SPAST mutations. While C9ORF72 ALS is characterized by RNA dysregulation, nucleocytoplasmic transport defects, and TDP-43 pathology, SPG4 has primarily been viewed as a disorder of microtubule severing and axonal transport. Despite distinct etiologies, both diseases selectively affect corticospinal neurons and cause progressive motor impairment. To identify convergent disease mechanisms, we generated cortical organoids (COs) and spinal organoids (SpOs) from C9ORF72 and SPAST mutant hiPSC lines. Immunohistochemical analysis revealed increased total TDP-43 and prominent cytoplasmic mislocalization in both mutant COs and SpOs compared with controls. Protein analysis revealed elevated TDP-43 abundance in diseased lines, whereas all control lines showed comparable expression levels, and all lines showing multiple bands, suggesting the presence of distinct isoforms. Loss of nuclear TDP-43 promotes cryptic exon inclusion through impaired RNA splicing, leading us to evaluate our organoids for cryptic exon expression. Preliminary data indicates the presence of varying levels of STMN2 and HDGFL2 cryptic exons in diseased lines with similar expression across controls. In parallel, we developed a corticospinal assembloid model to investigate differential cortical and spinal contributions to disease pathology. Together, these studies establish human organoid and assembloid platforms for defining shared TDP-43-dependent mechanisms across genetically distinct neurodegenerative disorders.

Disclosures: M. Lindner-Jackson: None. **S. Ramakrishnan:** None. **D.A. Bosco:** None. **L. Qiang:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.27/X29

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

Title: The role of TMEM106B in lysosomal biology

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Abstract: Transmembrane protein 106B (TMEM106B) is a critical regulator of lysosomal biology, and genetic variants at the TMEM106B locus are among the strongest known modifiers of risk for frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), particularly in GRN mutation carriers. Despite its prominent genetic link to neurodegeneration, the physiological role of this type II transmembrane protein and the mechanisms by which its dysfunction drives disease have only recently begun to emerge. Under physiological conditions, TMEM106B localizes to the late endolysosomal compartment where it modulates lysosomal morphology, acidification, and retrograde trafficking. We demonstrate that loss of TMEM106B leads to lysosomal enlargement, consistent with observations made by others. Interestingly,the C-terminal fragment (CTF) of TMEM106B, which gets cleaved in the lysosomal lumen, assembles into amyloid fibrils in the brains of aged individuals and patients across a spectrum of neurodegenerative diseases, including FTLD, Alzheimer's disease (AD), and Parkinson's disease (PD). The lysosomal cleavage of TMEM106B is poorly understood due to the lack of tools to detect TMEM106b cleavage. We developed a novel antibody that specifically detects the cleaved CTF of TMEM106B. We found the abundance of the CTF to vary across tested cell lines. Understanding the transition from functional membrane protein to pathological fibril is essential for developing therapeutic strategies targeting TMEM106b cleavage.

Disclosures: S. Coveney: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **R. Gray:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **R.W. Cho:** A. Employment/Salary (full or part-time):; Cell Signaling Technology.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.28/X30

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

Support: NIH Grant NS114326
NSF Grant 2425982

Title: Exploring the Changes on Histone H4 Post-Translational Modifications Associated within [PIN+] States

Authors: *K. SURVE[1], M. TORRENTE[2];
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Abstract: Prions are self-replicating, alternatively folded proteins that can induce other molecules of the same protein to change conformation into the alternative fold. In humans, prions are well established to cause fatal neurodegenerative diseases, however, in yeast, prions often aid in environmental adaptation. Mechanisms linking prion states to phenotypic variation still remain incompletely understood. To address this gap, we turn to epigenetics, the study of alterations in gene expression independent of DNA sequence. Epigenetic mechanisms include post translational modifications (PTMs) on histone proteins which act as regulators for gene utilization. Histones H3 and H4 are two of the core proteins present in the structure of a nucleosome. These histones have the ability to undergo multitudes of PTMs on their N-terminal tails (including acetylation and methylation), and can act as key regulators of gene expression and epigenetics. Rnq1 (Rich in Asparagine (N) and Glutamine (Q) 1) is the yeast prion protein responsible for the [PIN+] prion state, but much of its function in the native and prion states has not been discovered. Previous findings show that [PIN+] is associated with a decrease in Histone H3 marks involved in transcriptional activation. Here, we investigate PTMs on Histone H4 to determine whether PTM changes are linked to [PIN+], aiming to further understand the connection between prion biology and epigenetic regulation. Thus far, we have revealed a decrease in H4R3me2sym levels associated with [PIN+]. Ultimately, these findings will help provide insight into how yeast prions potentially influence gene expression, and contribute to understanding the potential adaptive advantages of the [PIN+] state.

Disclosures: K. Surve: None. **M. Torrente:** None.

Poster

PSTR308: Tauopathies, Synucleinopathies, and Other Related Diseases: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR308.29/X31

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

Support: R01AG071512

Title: Cystathionine Gamma-Lyase Modulates Neurogenesis and Cognitive Function Through Neurotrophin Signaling

Authors: *S. CHAKRABORTY[1], S. J. TRIPATHI[1], E. VAZQUEZ-ROSA[2], M. FILIPOVIC[4], S. H. SNYDER[5], A. A. PIEPER[3], B. D. PAUL[1];
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Abstract: The reverse transsulfuration pathway comprises enzymes that regulate the levels of glutathione, homocysteine, and the gasotransmitter hydrogen sulfide (H_2S), all of which are essential for brain homeostasis. In the central nervous system, these molecules contribute to the regulation of cerebral blood flow, maintenance of blood-brain barrier integrity, neuroplasticity, and redox balance. A key enzyme in this pathway is cystathionine γ-lyase (*Cth*), the primary neuronal source of the semi-essential amino acid cysteine and H_2S. H_2S modulates protein function through sulfhydration of reactive cysteine residues, a post-translational modification implicated in neurodegenerative disorders. However, the mechanisms linking *Cth*-derived H_2S signaling to neuronal health remain incompletely understood. To address this question, we performed a systematic characterization of $Cth^{-/-}$ mice, examining cognition, neurogenesis, neurotrophic signaling, and neuropathological changes. *Cth* deficiency resulted in early-onset neurodegeneration and was accompanied by increased oxidative stress, reduced neurogenesis, and related pathological alterations in neurotrophic signaling and the blood-brain barrier. These molecular and cellular changes were associated with behavioral abnormalities and dysregulated stress responses. Collectively, our findings identify *Cth* as a critical regulator of brain function and cognitive performance through its role in maintaining neurogenesis and neuronal homeostasis. Disruption of *Cth*-dependent pathways promotes neurodegeneration and contributes to the development of behavioral and cognitive impairments.

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Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.01/X32

Topic: C.06. Neuromuscular Diseases

Title: WWOX loss and mutation promote oxidative stress in amyotrophic lateral sclerosis

Authors: *S. Q. ZHANG[1], T. PETROZZIELLO[1], E. J. GRANUCCI[1], A. CASTILLO-TORRES[1], R. B. MONSANTO[1], S. S. HUNTRESS[1], C. R. CASHMAN[1], E. A. BORDT[2], C. D.

BLACKSTONE[1], M. E. CUDKOWICZ[1], J. D. BERRY[1], R. MOURO PINTO[1], G. SADRI-VAKILI[1];
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Abstract: Oxidative stress has been implicated in motor neuron degeneration in amyotrophic lateral sclerosis (ALS). However, the exact molecular mechanisms underlying increased reactive oxygen species (ROS) in ALS are not fully understood. In this context, an interesting candidate is the WW domain containing oxidoreductase (WWOX), a multifunctional protein that regulates various cellular pathways, including stress responses and mitochondrial function through its short-chain dehydrogenase/reductase (SDR) domain. WWOX has been implicated in several neurodegenerative and neurological diseases, but its role in ALS remains unclear. Here, we investigated whether WWOX contributes to ALS-associated oxidative stress. Leveraging the Project MinE dataset, we identified rare ALS-specific variants in *WWOX*, including a 261E stop codon mutation within the mitochondrial binding region of the SDR domain. To determine the functional consequences of this mutation, human neuroblastoma SH-SY5Y cells were treated with a recombinant protein carrying the 261E mutation ($rWWOX^{261E}$). $rWWOX^{261E}$ reduced cell viability and increased mitochondrial ROS, as measured by MTT and aconitase activity assays, respectively. To further investigate effects on mitochondrial function, SH-SY5Y cells were transfected with a plasmid encoding the mutant protein. However, expression of the 261E mutation did not alter basal respiration or ATP production, as measured by Seahorse Mito Stress assay. The increase in mitochondrial ROS was consistent with the reduction in cytochrome c oxidase we observed in ALS post-mortem motor cortex (mCTX). Notably, we also found a significant decrease in WWOX levels in ALS in the same cohort. To determine the consequences of loss of WWOX, its expression was reduced using a small interference RNA (siRNA) approach (siWWOX) in SH-SY5Y cells. siWWOX significantly increased both cytosolic and mitochondrial ROS, as determined by CellROX and aconitase activity assays. Treatment of SH-SY5Y cells with ALS mCTX lysates exhibiting the lowest WWOX levels induced ROS accumulation. Conversely, increasing WWOX levels through a recombinant full-length WWOX protein or WWOX overexpression mitigated ROS accumulation in ALS mCTX-treated cells. These effects occurred without detectable changes in basal respiration or ATP production. Collectively, our results demonstrate that the 261E stop codon mutation and overall loss of WWOX in ALS contribute to increased ROS, suggesting that increasing WWOX may mitigate oxidative stress in ALS.

Disclosures: S.Q. Zhang: None. **T. Petrozziello:** None. **E.J. Granucci:** None. **A. Castillo-Torres:** None. **R.B. Monsanto:** None. **S.S. Huntress:** None. **C.R. Cashman:** None. **E.A. Bordt:** None. **C.D. Blackstone:** None. **M.E. Cudkowicz:** None. **J.D. Berry:** None. **R. Mouro Pinto:** None. **G. Sadri-Vakili:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.02/Y1

Topic: C.06. Neuromuscular Diseases

Support: NIEH Grant #R01TS000331
10x Genomics Pilot Research Fund

Title: Distinct extracellular matrix remodeling in sporadic amyotrophic lateral sclerosis

Authors: *E. MOSTAFA[1,2,3], K. A. CORNELL[2], A. G. J. SKORPUT[2,3], E. STOMMEL[2]; [1]Integrative Neurosci., Dartmouth Col., Hanover, NH; [2]Neurol., Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [3]Mol. and Systems Biol., Geisel Sch. of Med. at Dartmouth, Hanover, NH

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron degeneration. While familial ALS (fALS) is linked to defined genetic mutations, more than 90% of ALS cases are sporadic (sALS) and do not have a known cause. Epidemiologic studies have implicated environmental and occupational exposures in sporadic ALS; however, the molecular pathways that link environmental exposures to ALS pathology remain poorly understood. To identify possible exposure-driven pathways associated with sporadic ALS, we generated a human motor cortex (BA4) spatial transcriptomic dataset and integrated it with a published single-cell RNA sequencing dataset from sporadic ALS, C9orf72-associated ALS, and pathologically normal control tissue. These unbiased analyses identified extracellular matrix (ECM) remodeling as a prominent pathway selectively enriched in sALS. Given the prolonged turnover, signaling capacity, and composition of the ECM, these findings suggest that ECM-associated mechanisms may represent an important interface between chronic environmental exposure and disease pathogenesis in sporadic ALS. Among ECM-associated genes, Tenascin-C (TNC) emerged as the most upregulated transcript in sALS tissue compared to fALS tissue. Cell clustering and annotations localized this signature to reactive astrocytes. Preliminary immunohistochemical analyses of postmortem motor cortex tissue further demonstrated increased TNC in sALS motor cortex. Ongoing studies are evaluating cerebrospinal fluid-associated ECM markers to determine whether this remodeling program may yield accessible biomarkers of sporadic disease. Collectively, these findings suggest that persistent ECM remodeling may represent a defining pathological feature of sporadic ALS and provide insight into how environmental exposure is translated into chronic neurodegenerative signaling.

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Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.03/Y2

Topic: C.06. Neuromuscular Diseases

Support: AMED-PRIME JP24gm6910013
AMED-MS7 JP24zf0127010

Title: Glial metabolic states in human sporadic amyotrophic lateral sclerosis uncovered by spatial single-cell proteomics.

Authors: *K. UEMURA[1], M. HIKOSAKA[3], M. KINOSHITA[2], M. HOSSAIN[5], S. PUNYAWATTHANANUKOOL[6], M. YOSHIDA[7], T. TSURUYAMA[2], G. OHTSUKI[4]; [1]Kyoto Univ. Grad. Sch. of Med., Kyoto-shi, Kyoto, Japan; [2]Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [4]Dept. of Drug Discovery Med., [3]Kyoto Univ., Kyoto, Japan; [5]Dept. of Neuroinflam. and Brain Fatigue Sci., Kyushu Univ. 88B, Fukuoka-Shi, Japan; [6]Mahidol Univ., Nakhon Pathom, Thailand; [7]Aichi Med. Univ., Nagakute, Aichi, Japan

Abstract: Sporadic amyotrophic lateral sclerosis (ALS) is characterized by selective motor neuron vulnerability accompanied by prominent glial responses, yet their molecular heterogeneity and spatial organization in the human central nervous system and spinal cord remain incompletely defined. Here, we delineate ALS-associated glial states in situ by spatially resolved using imaging mass cytometry (Hyperion^{TM}, Standard BioTools), single-cell proteomic profiling of postmortem human sporadic ALS and non-neurological control tissues across the motor cortex, spinal cord, and cerebellum. We identify subpopulations of astrocytes and microglia co-expressing both canonical ALS markers, phosphorylated TDP-43 and UBQLN2, together with co-enriched proteomic features, including IL6ST, TREM2, p53 and glutaminase (GLS). These glial states are consistent with transcriptomic signatures characterized by *TP53* and *GLS* upregulation, indicating convergence on senescence stress- and glutamine metabolism-related pathways. Notably, p53-GLS-associated profiles are selectively enriched in anatomically vulnerable regions in ALS, supporting region-specific glial metabolic alterations in human disease. DNA damage response suggested to cause glutamine metabolism alterations in aged iPSC-derived astrocyte culture. Together, these findings provide spatial proteomic evidence that previously known p53 activation in ALS preferentially localizes to reactive glia and is coupled to GLS-associated metabolic remodeling in ALS-affected human tissue. (Research Square 2026, doi.org/10.21203/rs.3.rs-9006017/v1)

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Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.04/Y3

Topic: C.06. Neuromuscular Diseases

Title: Leveraging public control for rare variant analysis of ALS Compute study identifies novel candidate risk genes for Amyotrophic Lateral Sclerosis

Authors: ***G. WU**[1], W. CHEN[2], S. TITHI[3], A. BRUSATI[4], P. KEAGLE[4], J. TAYLOR[3], J. LANDERS[4];
[1]Pathology, St Jude Children's Res. Hosp., Memphis, TN; [2]Quantitative Hlth. Sci., Mayo Clin., Rochester, MN; [3]Cell Mol. Biol., St. Jude Children's Res. Hosp., Memphis, TN; [4]Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder without cure. Although over 90% of ALS patients shared common molecular phenotype of TDP-43 proteinopathies, its genetic basis remains elusive, largely due to its heterogeneity, especially for sporadic ALS. Recent large case and control studies in a few big consortia only identified several potential new ALS genes. In this study, we performed gene-based rare variant burden analyses of nearly 4,500 ALS patients collected in ALS Compute using our pipeline, CoCoRV-nf, which leverages large external sequencing resources such as gnomAD v4 as controls. We identified 364 familial ALS (fALS) cases based on whether there is reported familial history or related individuals in our study then assigned the remaining as sporadic ALS (sALS, n=4,132). Related individuals were excluded from the analysis, so only one representative individual was kept in the fALS analysis. Ancestry-matched gene-based rare variant burden analyses using ~700,000 gnomAD v4 exomes as controls showed no evidence of systematic inflation. We not only confirmed the previous well known ALS genes (SOD1, TBK1, NEK1, TARDBP, OPTN, FUS), but also showed that a few top genes (TTC3, CENPE, GSTA1, FKBP15, CNOT6, PRADC1, LIPA, HSPA8, GDI2, RPE) significantly enriched with rare variants in the recent report (Hop 2026) were also significant in our analysis. In particular, RPE, an enzyme with metal ion binding activity, is significant in both fALS (P=0.0046) and sALS (P=0.0362). In addition, we were able to confirm that *HNRNPA1* was significant in fALS but not sALS (P= 0.0034 from two new independent families in ALSCompute). Moreover, we identified multiple pleckstrin homology domain containing genes (CNKSR1, P=0.0002; PLEKHM2, P=0.0009; PLEKHO1 P=0.0018 and PLEKHB1, P=1.372E-07) significantly enriched with rare variants in fALS or sALS patients. Among them, PLEKHO1 was significant (P=0.0092) in the gene-based burden test in Hop 2026. Another notable significant gene that was replicated in recent study is PCDHB12 (P=7.665E-05, vs P=0.0019 in Hop 2026). Our analyses showed that as the sample size of controls increases, we will be able to discover more ALS genes explaining the remaining inheritability. The large public control databases such as UKBiobank, AllofUS and gnomAD serve as great surrogates when the inflation is well controlled in rare variant burden tests using CoCoRV framework.

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Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.05/Y4

Topic: C.06. Neuromuscular Diseases

Support: 05.35219.6010.00000.202294.00000

Title: NEIMY-associated KIF5A mutation impairs mitochondrial transport

Authors: *H. L. CRABLE[1], J. R. BRENT[2];
[1]Neurol., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurol., Univ. of Pittsburgh Sch. Of Med., Pittsburgh, PA

Abstract: Mutations in KIF5A, a neuron-enriched kinesin-1 heavy chain critical for anterograde axonal transport, cause two clinically distinct disease: Amyotrophic Lateral Sclerosis (ALS) and Neonatal Intractable Myoclonus (NEIMY). Despite arising from frameshift mutations in the same regions of KIF5A's C-terminal domain, these disorders present with divergent clinical phenotypes. ALS-associated KIF5A has been well-characterized; the distribution and intracellular impact of NEIMY-associated KIF5A remain unknown. To investigate these phenotypic differences, we expressed WT, ALS, and NEIMY KIF5A variants in NSC34 motor neuron-like cells and assessed their effects on cargo-complex assembly and intracellular distribution. RPE cells lacking kinesin heavy chain (KIF5B KO) were used to isolate cargo-complex formation independently of endogenous motor competition. Both ALS and NEIMY variants showed abnormal accumulation at the neurite tip with corresponding somatic depletion, indicating disrupted autoinhibition. NEIMY KIF5A uniquely formed large aggregates associated with axonal swelling and cytoskeletal damage. In KIF5B KO cells, NEIMY KIF5A showed reduced co-localization with the mitochondrial adaptor Trak2, suggesting impaired cargo-complex assembly. Mitochondrial transport was dysregulated in a mutation-specific manner for both variants. Together, these findings demonstrate that ALS and NEIMY KIF5A variants disrupt motor function through distinct mechanisms — including altered autoinhibition, impaired cargo-complex formation, and differential effects on mitochondrial trafficking — providing new insight into the molecular basis of KIF5A-linked neurodegeneration and epilepsy.

Disclosures: H.L. Crable: None. **J.R. Brent:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.06/Y5

Topic: C.06. Neuromuscular Diseases

Support: NINDS Intramural Funding

Title: Loss of R-loop homeostasis caused by senataxin mutation disrupts local and distal transcription regulation in ALS4 motor neurons

Authors: *J. J. BUSSGANG[1], K. R. JOHNSON[2], C. GRUNSEICH[1];
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Abstract: During transcription, RNA can anneal to DNA forming DNA/RNA hybrids called R-loops. These R-loops cover 2-12% of the genome and can regulate transcription. R-loops are commonly dysregulated in motor neuron diseases such as C9orf72 ALS, spinal muscular atrophy, and ALS4 caused by dominant mutation of SETX (senataxin), an R-loop helicase. Beyond local effects, R-loops can bridge enhancers and distal promoters to sustain long-range gene expression like at the protocadherin alpha (PCDHA) cluster. This locus codes for alternatively spliced neuronal recognition genes, and variable promoters compete for a shared enhancer, where an enhancer R-loop is required for expression. Despite their importance, the distribution of R-loops in motor neurons, their disease-associated alterations, and how these alterations impact transcription and function, remain unanswered questions.
To map the R-loop landscape in iPSC-derived motor neurons (iMN) we performed CUT&Tag with S9.6, an R-loop specific antibody. R-loops covered 8% of the genome and were enriched at predicted R-loop forming sequences ($z>80$, permutation test $p<0.001$). Isogenic iMNs CRISPR edited to carry the ALS4-associated SETX L389S mutation showed R-loop alterations at Rho-GTPase and axonogenesis genes. RNA-sequencing implicated similar pathways, and differentially expressed genes were enriched near altered R-loops (OR: 1.75, $p=7.8\times10^{-8}$). PCDH genes were among the top transcriptomic hits and were broadly reduced, with PCDHA showing distance-dependent loss of expression. R-loops were also reduced at this locus at both the shared enhancer and the most distal promoters. To test R-loop regulation of PCDHA, we overexpressed RNaseH1 to reduce overall R-loop levels and measured PCDHA2, PCDHA6 and PCDHA7 by qRT-PCR. Expression of PCDHA genes fell to <1%, 52%, and 68% (all $p<0.002$) of control levels respectively, supporting distance-dependent sensitivity to R-loop loss. Consistent with disrupted PCDH regulation and altered expression of axonogenesis genes, L389S iMNs exhibited 62% longer neurites and reduced branch angle ($p<0.0001$).
Together, these data establish the first motor neuron R-loop map and reveal that ALS4-associated SETX mutation disrupts R-loop dependent transcriptional regulation at both local genes and long range enhancer regulated loci. By connecting R-loop redistribution to axonogenesis gene dysregulation, impaired PCDHA expression, and abnormal neurite morphology, this work implicates loss of senataxin-mediated R-loop homeostasis in motor neuron vulnerability in ALS4.

Disclosures: J.J. Bussgang: None. **K.R. Johnson:** None. **C. Grunseich:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.07/Y6

Topic: C.06. Neuromuscular Diseases

Title: Characterizing the association between tau and RNA-binding proteins in C9ORF72 amyotrophic lateral sclerosis

Authors: *T. PETROZZIELLO[1], H. XU[3], E. GRANUCCI[4], D. GAO[5], J. BERRY[1], M. CUDKOWICZ[1], G. SADRI-VAKILI[2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is increasingly recognized as a disorder of RNA-binding proteins (RBPs), yet the mechanisms that drive RBP mis-localization, aggregation, and persistence of pathological inclusions remain poorly understood. Recent studies suggest that the microtubule-associated protein tau may participate in biomolecular condensation and influence the organization of protein assemblies involved in cellular homeostasis. Although best known for its role in tauopathies, tau has also been implicated in ALS. We previously reported a selective increase in tau and phosphorylated tau in post-mortem motor cortex from individuals with C9ORF72-ALS (C9-ALS), the most common genetic form of ALS characterized by prominent RBP pathology. Building on these findings, here we investigated whether tau dysregulation is associated with RBP pathology in C9-ALS. Analysis of RNA sequencing (RNA-seq) datasets from the New York Genome Center ALS Consortium revealed no significant changes in *MAPT* transcript abundance across post-mortem motor cortex, cervical and lumbar spinal cord, cerebellum and frontal cortex in C9-ALS. In contrast, significant *MAPT* splicing alterations were detected in cervical spinal cord, cerebellum, and frontal cortex, suggesting that tau dysregulation in C9-ALS may occur at the level of RNA processing rather than gene expression. Additionally, tau displayed altered subcellular localization in post-mortem C9-ALS motor cortex, with increased nuclear pTau-S396 detected by biochemical fractionation and confirmed by RNAscope analyses. Strikingly, tau-positive fibrils accumulated in a distinctive perinuclear distribution in close proximity to nuclear TDP-43, a defining pathological hallmark of ALS. Co-immunoprecipitation studies further demonstrated an interaction between tau and TDP-43 in ALS motor cortex. Together, these findings identify a previously unrecognized association between tau pathology and TDP-43 in C9-ALS. Ongoing studies are determining whether similar interactions extend to additional ALS-linked RBPs to further define the role of tau in RBP pathology in ALS.

Disclosures: T. Petrozziello: None. **H. Xu:** None. **E. Granucci:** None. **D. Gao:** None. **J. Berry:** None. **M. Cudkowicz:** None. **G. Sadri-Vakili:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.08/Y7

Topic: C.06. Neuromuscular Diseases

Title: Microglial GLS1 inhibition ameliorates ALS-associated cognitive impairment

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Abstract: Microglial GLS1 inhibition ameliorates ALS-associated cognitive impairment Jiamin Li[1], Yannan Li[1], Naigang Li[1], Tomáš Tichý[2], Pavel Majer[2], Barbara S. Slusher[3,4], Xiaolei Zhu[1]1Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, [2]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic v.v.i., [3]Johns Hopkins Drug Discovery, [4]Department of Neurology, Johns Hopkins University

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with marked clinical heterogeneity. In addition to motor neuron degeneration, cognitive impairment is increasingly recognized as part of the ALS spectrum and predicts worse clinical outcomes. However, the mechanisms underlying ALS-associated cognitive impairment remain unclear.

Using public human brain snRNA-seq datasets, we identified GLS-positive microglia and compared their abundance and transcriptional features across diagnostic groups. To assess functional relevance, SOD1-G93A (SOD1) mice were treated with our recently developed hydroxyl-dendrimer-conjugated GLS1 inhibitor, Dendrimer-TTM020 (D-TTM020), or vehicle, with WT mice as controls. Behavioral performance was assessed at week 8 before treatment and reassessed at weeks 10 and 12. Cognitive function was assessed using Y-maze, novel object recognition (NORT), and social interaction tests (SIT); locomotor activity and motor function were assessed by open field test (OFT), grip strength, and rotarod.

Human brain snRNA-seq analysis showed an increased proportion of GLS-positive microglia in ALS patients with cognitive impairment, but not in ALS patients without cognitive impairment. GLS-positive microglia were enriched for glutaminolysis, phagocytosis, and complement pathways, suggesting a metabolically reprogrammed, phagocytic microglial state. In SOD1 mice, no baseline behavioral differences were observed among groups. From weeks 10 to 12, vehicle-treated SOD1 mice developed deficits in working memory, object recognition memory, and social recognition memory, which were ameliorated by D-TTM020 at both time points. OFT revealed no locomotor or anxiety-related confounding effects. Vehicle-treated SOD1 mice also developed motor deficits, including reduced grip strength and rotarod performance, both of which were improved by D-TTM020.

Together, these findings identify GLS-positive microglia as a microglial state associated with ALS-related cognitive impairment and support microglial GLS1 inhibition as a potential therapeutic strategy.

Disclosures: J. li: None. **Y. Li:** None. **N. li:** None. **P. Majer:** None. **B.S. Slusher:** None. **X. Zhu:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.09/Y8

Topic: C.06. Neuromuscular Diseases

Support: NIH, NINDS, NS110953
Les Turner ALS Foundation

Title: Riluzole unexpectedly induces hyperexcitability while normalizing motoneuron size in presymptomatic ALS

Authors: *A. MAHROUS[1,2], B. HEIT[2], C. HECKMAN[2,3,4];
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Abstract: Riluzole is the most widely used therapy for amyotrophic lateral sclerosis (ALS) and is thought to confer neuroprotection by suppressing motoneuron excitability and glutamate release. However, clinical observations show that these suppressive effects diminish with continued treatment. We tested the hypothesis that dysregulated homeostasis in ALS counteracts riluzole action. Presymptomatic SOD1^G93A (mSOD1) mice received therapeutic doses of riluzole for 10 days, after which motoneuron properties were assessed using intracellular recordings in the isolated sacral spinal cord. Contrary to its expected suppressive actions, chronic riluzole resulted in enhanced intrinsic excitability and polysynaptic excitatory inputs in mSOD1 motoneurons, while having no detectable effect in wild-type (WT) controls. Increased motoneuron excitability was evident as elevated frequency-current (F-I) gain, enhanced persistent inward currents, and a shift toward more excitable firing phenotypes. Notably, these changes persisted even when riluzole was reintroduced acutely ex vivo, indicating that adaptive responses are not readily overcome by continued drug presence. In parallel, riluzole reduced motoneuron membrane capacitance in mSOD1 mice to the range observed in WT animals, consistent with normalization of cell size. This reduction in size, together with elevated intrinsic currents, suggests a coordinated remodeling of passive and active properties that shape overall excitability. These findings demonstrate that hyperactive homeostatic mechanisms in ALS overcompensate for riluzole-induced suppression, resulting in paradoxical hyperexcitability. At the same time, normalization of motoneuron size suggests a distinct mechanism that may reduce metabolic demand and contribute to neuroprotection. Together, this work reframes riluzole's functional impact and identifies dysregulated homeostasis as a key determinant of therapeutic response in ALS.

Disclosures: A. Mahrous: None. **B. Heit:** None. **C. Heckman:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.10/Y9

Topic: C.06. Neuromuscular Diseases

Support: Laurence and Sandi Gluck Charitable Foundation

Title: Spatial transcriptomic profiling of degenerating motor neurons in a sporadic ALS CSF-mediated animal model

Authors: *J. K. WONG[1], D. KANGRIWALA[1], A. GRINBERG MITIDIERI[1], L. APELTSIN[2], S. A. SADIQ[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by motor neuron degeneration. Sporadic amyotrophic lateral sclerosis (sALS) is the predominant subtype which arises without family history. We previously developed a mouse model for sALS via intrathecal delivery of sALS cerebrospinal fluid (CSF) (Wong et al., 2022). sALS CSF, but not familial ALS CSF, induced motor disability, widespread degeneration of motor neurons and TDP-43 mislocalization in mice. sALS CSF neurotoxicity was mediated by apolipoprotein B-100 (ApoB), a cholesterol transporter which binds to low-density lipoprotein receptor (LDLR). Our recent studies revealed that LDLR is necessary for sALS CSF/ApoB-mediated motor neuron degeneration. However, the precise molecular mechanisms contributing to sALS CSF-induced motor neuron degeneration are unknown. This study aimed to identify transcriptomic signatures of motor neurons undergoing sALS CSF-induced degeneration. Adult female C57BL/6J mice underwent laminectomies at cervical levels 4 and 5, then received intrathecal injections into the subarachnoid space delivering 3µL of: 1) sALS CSF, 2) healthy control (HC) CSF, or 3) primary progressive multiple sclerosis (PPMS) CSF. Forelimb motor function was evaluated at 1 day post injection, then mice were perfused with 4% paraformaldehyde. Cervical spinal cords were processed for spatial transcriptomic profiling using the 10X Genomics Visium HD platform. Motor assessments and transcriptomic analyses were performed blinded. Mice injected with sALS or PPMS CSF had significantly impaired forelimb function compared to HC CSF-injected mice, but motor neuron loss was specific to sALS CSF-injected mice. Only sALS CSF induced significant downregulation of certain genes previously reported to be downregulated in sALS patient motor neurons, including: *NEFL* (neurofilament light chain), *MBP* (myelin basic protein), and *SLC1A2* (glutamate transporter-1). Noteworthy genes upregulated by sALS CSF include *YWHAH* (14-3-3 eta) which has been shown to colocalize with TDP-43 in sALS patient spinal cords and regulates various functions such as receptor trafficking and cell survival, and *ISL1* (Islet-1) which is critical for motor neuron survival and regulates lipid metabolism. Gene set enrichment analysis revealed an upregulation of cholesterol biosynthesis genes in sALS CSF-injected mice. Overall, our data show that motor neurons in sALS CSF-injected mice exhibit a disease-specific neurodegenerative transcriptomic signature similar to that observed in sALS patients and identify candidate genes linking cholesterol dysregulation to cell death.

Disclosures: J.K. Wong: None. **D. Kangriwala:** None. **A. Grinberg Mitidieri:** None. **L. Apeltsin:** None. **S.A. Sadiq:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.11/Y10

Topic: C.06. Neuromuscular Diseases

Support: NIH/NINDS MPI award to C.L. Lorson and M.A. Lorson (R01NS134816)

Title: Examining how IGHMBP2 truncating mutations modulate disease pathology in mouse models based on IGHMBP2 patient mutations of SMARD1/CMT2S

Authors: *T. MONY[1,2], R. MUCHOW[1,2], F. LLORENTE TORRES[1,2], C. LORSON[1,2], M. LORSON[1,2];
[1]Dept. of Pathobiology and Integrative Biomed. Sciences, Col. of Vet. Med., [2]Bond Life Sci. Ctr., Univ. of Missouri, Columbia, MO

Abstract: Mutations in immunoglobulin mu DNA binding protein 2 (*IGHMBP2*) cause Spinal Muscular Atrophy with Respiratory Distress type 1 (SMARD1), a fatal infantile motor neuron disease with diaphragmatic paralysis, and Charcot-Marie-Tooth disease type 2S (CMT2S), a later-onset distal neuropathy without respiratory failure. The focus of these studies concerns two patient mutations, C496X and R605X. Both mutations are located within the IGHMBP2 helicase domain and are predicted to generate truncated proteins due to premature termination codons (PTCs). Interestingly, there are over 25 pathogenic PTC variants identified within IGHMBP2. C496X is one of the most prevalent IGHMBP2 mutations. In the homozygous recessive genetic context, C496X and R605X mutations present as SMARD1 while in compound heterozygous contexts C496X and R605X are associated with SMARD1 or CMT2S, suggesting that allelic mutations critically contribute to disease onset and severity. To investigate how these clinically relevant truncating alleles influence disease severity and pathology, we generated *Ighmbp2* mouse models harboring the corresponding C495X and R604X mutations. Homozygous and compound heterozygous mouse pups were born with litter sizes and genotype frequencies within expected ranges. To define genotype-phenotype relationships, we performed longitudinal neonatal assessments of survival, growth, feeding, and respiratory function. *Ighmbp2*$^{R604X/R604X}$ mutants developed postnatal failure to thrive, with a median survival of postnatal day 6 (P6) and 0% survival to P9. *Ighmbp2*$^{C495X/C495X}$ and *Ighmbp2*$^{C495X/R604X}$ mice showed a median survival of P9 and P8, respectively. Interestingly, while only 9% of *Ighmbp2*$^{R604X/R604X}$ survived to P7, 86% of *Ighmbp2*$^{C495X/C495X}$ and 90% of *Ighmbp2*$^{C495X/R604X}$ mice survived to P7. Mutant mice of all three genotypes displayed normal birth weights with milk sacs readily visible but rapidly developed growth impairment at P2, with marked divergence from wild-type littermates by P6. Disease progression was accompanied by significant deficits in suckling behavior as measured

by reduction in a milk sac. *Ighmbp2*$^{R604X/R604X}$ mice presented with respiratory distress and pathology of the phrenic nerve and diaphragm muscle fibers with signs of milk aspiration and lung pathology. We are characterizing respiratory deficits in *Ighmbp2*$^{C495X/C495X}$ and *Ighmbp2*$^{C495X/R604X}$ mice by plethysmography as well as pathology associated with the phrenic nerve, diaphragm, and lungs. These studies are aimed at providing an understanding of how truncating mutations modify disease pathology and define the differences between SMARD1 and CMT2S.

Disclosures: T. Mony: None. **R. Muchow:** None. **F. Llorente Torres:** None. **C. Lorson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shift Pharmaceuticals. **M. Lorson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Shift Pharmaceuticals.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.13/Y12

Topic: C.06. Neuromuscular Diseases

Support: Stanford Dean's Postdoctoral Fellowship

Title: Axonal mitochondrial transport deficiency recapitulates neurodegenerative features of amyotrophic lateral sclerosis

Authors: *H. LIU[1], D. JIANG[2], M. LI[1], S. SU[1], D. LIU[3], Y. HU[4];
[1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Palo Alto, CA, ; [3]Stanford Ophthalmology, [4]Dept. of Ophthalmology, Stanford Univ., Palo Alto, CA

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal central nervous system neurodegenerative disease. Our previous study suggested that impaired axonal mitochondrial transport represents a shared molecular pathogenic mechanism underlying both glaucoma and ALS. Consistent with this finding, mitochondrial transport defects have been reported in multiple ALS models. To determine whether impaired mitochondrial transport is sufficient to drive ALS-like disease, we generated motor neuron-specific kinesin family member 5A (KIF5A) and kinesin family member 5B (KIF5B) double-knockout mice (ChAT-Cre::KIF5Af/f;KIF5Bf/f, referred to as DKO mice). Floxed littermates lacking Cre expression served as controls. Intrathecal delivery of pAAV-PHP.eB-CAG-DIO-MitoDsRed2 at postnatal day 0 followed by *in vivo* imaging revealed a marked reduction in axonal mitochondrial content and no detectable mitochondrial transport in sciatic nerves of DKO mice. We found that DKO mice exhibited a hindlimb clasping phenotype, body weight loss, reduced grip strength, and progressive impairments in rotarod and wire hang performance. Hindlimb kinematic analysis further revealed

significant reductions in step length, locomotor speed, and hindlimb joint angles in DKO mice at 20 weeks. Consistent with motor deficits, DKO mice exhibited reduced tibialis anterior and gastrocnemius muscle weights, decreased compound muscle action potential amplitudes, and reduced neuromuscular junction innervation. In addition, robust microglial and astrocytic activation was observed in the ventral horn of the spinal cord in DKO mice. To avoid developmental confounds and independently validate these findings in adult mice, we developed an AAV using a motor neuron-specific enhancer to achieve selective gene expression in lower motor neurons. Tissue-clearing approaches combined with Imaris-based 3D reconstruction showed that transgene expression was restricted to the ventral horn, selectively labeling lower motor neurons in both the lateral motor column and medial motor column. Delivery of rAAV-PHP.eB-CreT2AGFP into 4-week-old KIF5Af/f;KIF5Bf/f mice induced an even more severe phenotypes, resulting in a mean survival of 44.4 ± 1.5 days (mean ± SEM) post injection. Together, these findings establish a relevant ALS model and highlight axonal mitochondrial transport deficiency as a potential cause of ALS, marking an important advance in understanding and developing treatments for ALS.

Disclosures: H. Liu: None. **D. Jiang:** None. **M. li:** None. **S. Su:** None. **D. Liu:** None. **Y. Hu:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.14/Y13

Topic: C.06. Neuromuscular Diseases

Title: Tofersen Displays Cell Type-Dependent Pharmacodynamic Activity in the SOD1-ALS Mouse Spinal Cord After Intrathecal Delivery

Authors: *M. SHANMUGAM;
Biogen, Cambridge, MA

Abstract: Tofersen Displays Cell Type-Dependent Pharmacodynamic Activity in the SOD1-ALS Mouse Spinal Cord After Intrathecal Delivery *Shanmugam Muruganandan[†], Twinkle Chowdhury[†], Amanda J. Guise[†], Shukkwan K Chen, Michael Peterson, Maria I. Zavodszky, Ekta Kadakia, Thomas Carlile, Yuqing Liu, Zhengyu Ouyang, Di Jiang, Taras Tuczkewycz, Long Yuan, Patrick Trapa, Shih-Ching Lo.* Biogen, Cambridge, MA, USA.
[†]Contributed equally
Antisense oligonucleotides (ASOs) are a promising therapeutic strategy for amyotrophic lateral sclerosis (ALS), yet their cell-type-resolved pharmacodynamics in the spinal cord require systematic investigation across CNS cell types. Tofersen (Qalsody), an approved SOD1-targeting antisense oligonucleotide (ASO) in many countries, lowers SOD1 expression and neurofilament biomarkers in SOD1-ALS. However, the extent to which different cell types respond to

treatment remains unclear, representing an important factor that may influence therapeutic efficacy. Here, we integrated single-nucleus RNA sequencing, RNAscope in situ hybridization, immunohistochemistry, LC-MS/MS quantification, and biomarker analyses to map tofersen distribution and activity in the lumbar spinal cord of SOD1-G93A mice following intrathecal administration. Tofersen reduced SOD1 expression across all major CNS cell types, with distinct potency profiles, showing highest sensitivity in oligodendrocytes (IC_{50} 0.08 μg/g [snRNA-seq], 0.37 μg/g [RNAscope]), followed by astrocytes (0.43 μg/g [snRNA-seq], 1.8 μg/g [RNAscope]), microglia (0.53 μg/g [snRNA-seq], 2.0 μg/g [RNAscope]) and motor neurons (0.53 μg/g [snRNA-seq], 2.9 μg/g [RNAscope]). Microglia exhibited dose-dependent ASO-positive inclusions, consistent with altered intracellular handling or sequestration at higher exposure. Across 20-80 μg/mouse, SOD1 knockdown correlated with reductions in serum phosphorylated neurofilament heavy chain (pNF-H) and preservation of compound muscle action potentials, whereas effects plateaued at higher doses (160-320 μg/mouse). Collectively, these findings demonstrate widespread but heterogeneous cellular engagement of tofersen in the spinal cord and define a cell-type-resolved pharmacodynamic landscape that informs dosing, biomarker interpretation, and next-generation ASO design.

Disclosures: M. Shanmugam: None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.15/Y14

Topic: C.06. Neuromuscular Diseases

Support: NIH NINDS R01 NS110953

Title: Chronic diazepam reveals excessive homeostatic gain in SOD1G93A mouse spinal motoneurons

Authors: *E. REEDICH[1], Y.-T. CHEN[1], R. MANUEL[1], D. LI[1], M. MANUEL[2];
[2]Ryan Inst. for Neurosci., [1]Univ. of Rhode Island, Kingston, RI

Abstract: Motoneurons are under strong pressure to maintain stable motor output throughout an individual life, through homeostatic regulation of their electrical properties. Dysregulated spinal motoneuron excitability has long been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). Recent work in $SOD1^{G93A}$ mice suggests that the homeostatic response of motoneurons becomes dysregulated as cellular processes are disrupted by the disease, causing fluctuations in motoneuron electrical properties. Yet, few studies directly test whether ALS motoneurons respond differently than wild type motoneurons to a common chronic perturbation. Here, we used in vivo electrophysiology to test whether motoneurons from pre-symptomatic $SOD1^{G93A}$ mice modulate excitability differently than wild type motoneurons in response to the

same homeostatic perturbation: chronic inhibition exerted by the benzodiazepine diazepam. Using linear mixed-effects statistical models, we assessed whether diazepam treatment differentially modulated passive properties, firing behavior, spike properties, and/or synaptic inputs in $SOD1^{G93A}$ versus wild type motoneurons. We identified a significant genotype × treatment interaction effect selectively for properties related to passive membrane integration and spike initiation, including membrane time constant, peak input resistance, and recruitment current. In contrast, firing gain, spike waveform characteristics, and synaptic inputs were largely unaffected. These findings indicate that sustained inhibitory perturbation selectively triggered overactive intrinsic compensatory mechanisms in $SOD1^{G93A}$ motoneurons rather than inducing widespread changes in firing or synaptic transmission. Together, our results provide direct evidence for over-active homeostatic control of motoneuron excitability and support a view of motoneuron dysfunction in ALS as a problem of altered feedback regulation rather than simply hyper- or hypo-excitability.

Disclosures: E. Reedich: None. **Y. Chen:** None. **R. Manuel:** None. **D. Li:** None. **M. Manuel:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.16/Y15

Topic: C.06. Neuromuscular Diseases

Title: Disease-driven transcriptomic signatures of lumbar motoneurons in the SOD1*G93A mouse model of amyotrophic lateral sclerosis

Authors: *S. ANTONUCCI, M. R. ALKASLASI, M. LANDIS, H. SILBERBERG, J. WLASCHIN, C. E. LE PICHON;
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Abstract: ALS is a fatal neurodegenerative disease characterized by motoneuron (MN) loss. Over 20% of familial cases involve mutations in *SOD1* gene. To investigate disease-associated transcriptional changes, we performed single-nucleus RNA sequencing of lumbar MNs from hSOD1*G93A mice at multiple time points during disease progression, from pre-symptomatic to late stages. Skeletal MNs, especially alpha MNs, are the most vulnerable in ALS. Consistently, we observe that the magnitude of ALS-induced transcriptional changes, peaking at 10 weeks, matches this gradient of vulnerability. Among alphas, fast-firing MNs are the most susceptible, and their response also peaks at 10w. Importantly, two SOD1-specific subpopulations, a 'disease-primed' and an ‘injured’ one, seem to emerge from the fast-firing group, gradually downregulate MN markers and upregulate stress- and injury-related programs. Histological validation confirmed their markers and concordance with human ALS spinal transcriptomic datasets. Additionally, we assessed the abundance of ‘primed’ and ‘injured’ MNs, their correlation and

their survival, and we are currently defining their pathology and dynamics. Overall, this work defines the landscape of SOD1 ALS transcriptional MN changes and signatures of vulnerability. By identifying disease-associated states, we uncover mechanisms that are potentially conserved across ALS etiologies (beyond SOD1 ALS), and that may inform our understanding of this disease.

Disclosures: S. Antonucci: None. **M.R. Alkaslasi:** None. **M. Landis:** None. **H. Silberberg:** None. **J. Wlaschin:** None. **C.E. Le Pichon:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.17/Y16

Topic: C.06. Neuromuscular Diseases

Support: FIGHT-MND DIS-202403-01216

Title: LRP4 overexpression in muscle helps to stabilize postsynaptic specializations in ALS model mice.

Authors: *P. G. NOAKES[1], U. AGRAWAL[2], V. CHEN[4], K. K. CHAND[3], L. MEI[5], W.-C. XIONG[6], N. A. LAVIDIS[2];
[1]Sch. of Biomed. Sci., The Univ. of Queensland, St Lucia, Australia; [2]Sch. of Biomed. Sci., [3]UQ Ctr. for Clin. Res., The Univ. of Queensland, Brisbane, Australia; [4]Sch. of Biomed. Sci., Univ. of Queensland, Brisbane, Australia; [5]CIMR, Chinese Inst. for Med. Research, Beijing, Beijing, China; [6]Neurosciences, Case Western Reserve Univ., Cleveland, OH

Abstract: The Low-Density Lipoprotein Receptor-Related Protein 4 (LRP4) plays a critical role in the formation and maintenance of neuromuscular junctions (NMJs) such as the clustering of acetylcholine receptors, through its interaction with Muscle-Specific Kinase (MuSK). Previously, we have shown that cultured muscle cells from ALS patients have low levels of LRP4 when compared to muscle cells from healthy control patients. These low levels may in part explain why ALS muscle cells fail to cluster acetylcholine receptors is response to neural-agrin - the ligand for LRP4. We therefore investigated the effects of overexpressing LRP4 in the muscles of SOD1G93A ALS model mice. To overexpress LRP4 in skeletal muscle in SOD1G93A mice, we crossed Human Skeletal Actin (HSA)-LRP4 heterozygous females with heterozygote male SOD1G93A mice. This crossing generated strain control (wild type, [+/+]), LRP4/+, SODG93A/+, and SODG931-HSA-LRP4 double transgenic mice. At selected ages of ALS-like progression, hind limb muscles were assessed for muscle innervation and synaptic transmission. Innervation status was assessed using antibodies to components of the motor nerve terminal and fluorescently labeled alpha-bungarotoxin to locate post-synaptic acetylcholine receptors. Synaptic transmission was assessed by sharp electrode electrophysiology to record

spontaneous and evoked endplate potentials. Our results show that LRP4 overexpression in skeletal muscle preserved muscle innervation and NMJ synaptic transmission, particularly at the later stages of ALS-like symptoms. At the onset and mid-stage, SOD1G93A/HSA-LRP4 mice exhibited a slower decline in NMJ denervation compared to SOD1G93A mice. By the end stage, SOD1G93A/HSA-LRP4 mice retained significantly more innervated NMJs and fewer denervated NMJs compared to SOD1G93A mice, suggesting that LRP4 overexpression may help preserve NMJ integrity and function. Importantly, the overexpression of LRP4 in muscle of HSA-LRP4 mice did not result in any negative effects on NMJ morphology or function, indicating that LRP4 overexpression is well-tolerated in healthy muscle. These findings suggest that enhancing LRP4 expression can slow NMJ loss in ALS model mice. Current studies are underway to determine if this slowed loss also results in increased motor neuron survival, lower levels of reactive gliosis, and muscle inflammation. These findings may provide opportunities to explore combinatory approaches targeting LRP4 with other potential effector proteins from the neural-agrin signaling pathway to improve muscle strength in ALS.

Disclosures: P.G. Noakes: None. **U. Agrawal:** None. **V. Chen:** None. **K.K. Chand:** None. **L. Mei:** None. **W. Xiong:** None. **N.A. Lavidis:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.18/Y17

Topic: C.06. Neuromuscular Diseases

Title: A NOVEL MOUSE MODEL OF SPORADIC ALS RECAPITULATES SYSTEMIC EXTRACELLULAR VESICLE-MEDIATED PATHOLOGY

Authors: V. RICOTTI[1], R. ROSSI[1], V. MARIOT[2], M. FALZARANO[3], M. PERRONE[3], C. GIORGI[3], F. CERRI[4], V. SANSONE[4], T. IANNITTI[3], E. KRITIKOU[1], J. TOIVANEN[5], T. BRAGGE[5], P. SHAW[6], P. PINTON[3], J. DUMONCEAUX[2], ***T. VOIT**[7];
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Abstract: Background: Amyotrophic lateral sclerosis (ALS) is predominantly sporadic, yet most preclinical models rely on genetic mutations that represent only a minority of cases. More broadly, no existing animal model fully recapitulates the complexity of human neurodegenerative disease, contributing to the translational gap and high attrition rate in therapeutic development. Increasing evidence supports a role for systemic factors, including circulating extracellular vesicles (EVs), in disease propagation and phenotypic convergence across ALS subtypes.

Objective: To develop and characterise a translationally relevant mouse model of sporadic ALS driven by systemic exposure to patient-derived pathogenic factors contained in EV cargo.
Methods: A sporadic ALS-like phenotype was induced in immunocompromised NRG mice through systemic administration of EVs isolated from the serum of ALS patients or healthy controls (HC). Animals were longitudinally assessed using a comprehensive battery of behavioural and functional assays, including kinematic gait analysis (CatWalk) and motor coordination testing. Histopathological analyses of spinal cord and skeletal muscle were performed to evaluate motor neuron integrity and peripheral tissue involvement.
Results: Mice exposed to ALS EVs but not those exposed to HC EVs developed progressive neuromuscular impairment characterised by altered gait parameters, impaired hindlimb coordination, and decline in motor performance over time. Systemic exposure to patient-derived EV-associated factors was sufficient to induce ALS-like pathology in vivo, providing direct functional evidence of their pathogenic role. Histological evaluation confirmed motor neuron degeneration and muscle fibre pathology, supporting both central and peripheral involvement. The model demonstrated reproducible disease progression and robust, quantifiable functional readouts.
Conclusions: This novel model recapitulates key aspects of sporadic ALS by integrating systemic pathogenic extracellular vesicle-mediated mechanisms with measurable functional and histopathological outcomes. It provides a highly translational platform that extends beyond mutation-driven paradigms and supports the investigation of disease biology in a context reflective of the majority of ALS patients. These findings further support a pathogenic role for circulating factors in ALS and highlight EVs as both mechanistic drivers and potential therapeutic targets.

Disclosures: V. Ricotti: A. Employment/Salary (full or part-time):; Co-founder, CEO and shareholder, Vesalic Ltd. **R. Rossi:** A. Employment/Salary (full or part-time):; Employee and shareholder, Vesalic Ltd. **V. mariot:** Other; Shareholder, Vesalic Ltd.. **M. Falzarano:** None. **M. Perrone:** None. **C. Giorgi:** None. **F. Cerri:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **V. Sansone:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **T. Iannitti:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **E. Kritikou:** A. Employment/Salary (full or part-time):; Employee and optionholder, Vesalic Ltd. **J. Toivanen:** Other; Employee, Charles River Laboratories. **T. Bragge:** Other; Employee, Charles River Laboratories. **P. Shaw:** F. Consulting Fees (e.g., advisory boards); Consultant, Vesalic Ltd. **P. Pinton:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **J. Dumonceaux:** Other; Shareholder, Vesalic Ltd. **T. Voit:** Other; Co-Founder and Shareholder of Vesalic.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.19/Y18

Topic: C.06. Neuromuscular Diseases

Title: Profiling of cellular and molecular features in a mouse model of Amyotrophic Lateral Sclerosis using hyperplex spatial multiomics

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the loss of upper and lower motor neurons, leading to muscle weakness, paralysis, and ultimately respiratory failure (Beers et al., 2019). In addition to neuronal degeneration, increasing evidence highlights a critical role for neuroinflammation and immune responses in disease onset and progression. However, resolving the spatial organization of immune and structural alterations within the central nervous system remains a major challenge, limiting our understanding of the complex cellular interactions underlying ALS pathogenesis. Here, we applied a hyperplex multiomics workflow combining immunofluorescence and RNA in situ hybridization to enable simultaneous detection of protein and RNA targets within the same tissue section in an ALS mouse model. Fixed frozen sagittal brain sections from TAR6/6 transgenic mice overexpressing human TAR DNA-binding protein 43 (TDP-43) (Scherz et al., 2018) were processed using the automated COMET™ platform. This workflow integrates RNAscope™ HiPlex Pro (Wang et al., 2012) with sequential immunofluorescence (seqIF™) (Rivest et al., 2023) enabling RNA and protein detection within a single section. Image analysis using HORIZON™ software enabled single-cell quantification and spatial mapping of molecular phenotypes. The automated multiomics approach enabled simultaneous profiling of over 60 targets, including 12 RNA transcripts and more than 50 protein markers within the same tissue section. Hyperplex protein panels enabled mapping of major neural and non-neural cell populations, including neurons, astrocytes, microglia, oligodendrocytes, immune cells, together with markers of cellular activation, synaptic organization, metabolic function and vascular structure. Complementary RNA targets captured transcriptional programs related to neuronal integrity, glial function, and immune activation. Integration of these modalities enabled spatial profiling of cell types and molecular states. Tissue-wide analysis revealed region-specific increases in markers associated with glial activation, accompanied by signatures indicative of altered neuronal and synaptic function. Overall, this automated hyperplex spatial multiomics approach enables detailed, single-cell resolution mapping of molecular and cellular features in the ALS brain, providing a scalable workflow to study the spatial dynamics of neurodegeneration and neuroimmune interactions.

Disclosures: C. Saygili Demir: A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **M. Bonnet:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **J. Ballesteros:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **P. Machado Almeida:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **M. Procopio:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial. **S. Brajkovic:** A. Employment/Salary (full or part-time):; Bio-Techne Spatial.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.20/Y19

Topic: C.06. Neuromuscular Diseases

Title: TDP-43 Q331K overexpression leads to perturbed metabolic and circadian function in a mouse model

Authors: *E. H. JENSEN[1], S. GIERA[2], J. C. DODGE[3];
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Abstract: TDP-43 protein inclusions are pathological hallmarks of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). While metabolic and circadian dysregulation are prominent features of disease progression, the mechanisms by which TDP-43 pathology drives these disruptions remain unclear. We investigated how TDP-43 overexpression influences metabolism and circadian function using the *Prp-TDP-43-Q331K* mouse model, which harbors the familial ALS-associated Q331K mutation. Beginning at 3 months of age, Q331K mice exhibited ALS-like motor dysfunction, alongside FTD-like features including weight gain, hyperphagia, and reduced exploratory behavior. By 7 months, Q331K mice showed elevated plasma cholesterol and LDL levels with significant downregulation of cholesterol biosynthesis and oxidative phosphorylation pathway genes in spinal cord. Home cage monitoring and RAIN-based circadian analysis revealed markedly reduced activity and disrupted circadian gene expression in the lumbar/sacral spinal cord. These findings demonstrate that TDP-43 pathology can drive coordinated metabolic and circadian dysfunction in ALS/FTD.

Disclosures: E.H. Jensen: A. Employment/Salary (full or part-time):; Sanofi. **S. Giera:** A. Employment/Salary (full or part-time):; Sanofi. **J.C. Dodge:** A. Employment/Salary (full or part-time):; Sanofi.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.21/Y20

Topic: C.06. Neuromuscular Diseases

Support: RO1NS126191

Title: Spatial regulation of Stathmin-2: testing novel roles for TDP-43 pathology in mRNA trafficking and local translation

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is characterized by severe axonal degeneration and often fatal within five years of diagnosis. Cytoplasmic mislocalization of TAR DNA-binding protein 43 (TDP-43) occurs in ~97% of both sporadic and familial cases. When this occurs, it disrupts crucial RNA processing of a variety of proteins used for axonal maintenance, one of these being our protein of interest Stathmin-2 (Stmn2). Cytoplasmic mislocalization of TDP-43 creates a truncated, nonfunctional form of Stmn2 via cryptic splicing. For this reason, antisense oligonucleotides (ASOs) have been explored as a mechanism to prevent cryptic splicing of Stmn2. Restoring proper splicing via ASOs is a promising therapeutic approach, but it may fail to fully rescue distal axonal Stmn2. True protein homeostasis likely requires regulatory mechanisms beyond basic vesicular transport. Given TDP-43's endogenous role in RNA transport, we propose that during cytoplasmic mislocalization not only does it cause cryptic splicing of Stmn2, but also prevents movement of Stmn2 mRNA throughout peripheral axons for local translation. To investigate this, we employed compartmentalized microfluidic cultures of human iPSC-derived motor and sensory neurons. Using RNA-FISH, we have detected axonal Stmn2 mRNA puncta within mature motor and sensory neurons. These puncta colocalize with TDP-43 protein at a rate of 85.8%. Additionally, applying the translation inhibitor cycloheximide exclusively to the axonal compartment of sensory neurons resulted in a 34.6% reduction in overall axonal Stmn2 protein levels. To explore the role TDP-43 mislocalization may play in Stmn2 axonal translation, we are utilizing a Q331K TDP-43 mutant iPSC line. When this mutation is present, we see a 76.5% reduction in axonal Stmn2 mRNA compared to the wildtype control. Together, our data suggest that aberrant TDP-43 not only prevents proper nuclear RNA processing of Stmn2 but also critically disrupts its mRNA transport, acting as a secondary bottleneck that hinders local translation within the axon.

Disclosures: C. Lathrum: None. **D. Summers:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.22/Y21

Topic: C.06. Neuromuscular Diseases

Support: RO1NS091299-09

Title: TDP-43 Proteinopathy Impairs Glial Nascent Protein Synthesis In Vivo

Authors: *N. A. HALL[1], D. DE PAULA MOREIRA[2], B. CHAUHAN[2], R. SHARMA[3], B. LOVELL[3], P. PIRROTTE[3], D. C. ZARNESCU[2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron death leading to muscle atrophy, paralysis, and respiratory failure. Approximately 97% of ALS cases exhibit TDP-43 proteinopathy, characterized by cytoplasmic mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43). As a DNA/RNA-binding protein, TDP-43 plays critical roles in RNA processing and translational regulation; however, how TDP-43 proteinopathy alters protein synthesis in specific cell types and subcellular compartments remains incompletely understood. Moreover, while neuronal dysfunction has been extensively studied, the contribution of glial translational dysregulation to disease pathogenesis is less well defined. To investigate this, we expressed human wild-type (WT) or ALS-associated G298S TDP-43 in *Drosophila* glia and assessed nascent protein synthesis using Non-Canonical Amino acid Tagging (NCAT), which enables metabolic incorporation of labeled amino acids into newly synthesized proteins for visualization and enrichment. We applied fluorescent non-canonical amino acid tagging (FUNCAT) in third instar larval ventral nerve cords (VNCs) and neuromuscular junctions (NMJs). Bioorthogonal non-canonical amino acid tagging (BONCAT), which uses biotin-based enrichment of newly synthesized proteins, was performed in adult brains followed by immunoblot analysis. Expression of human TDP-43 in *Drosophila* glia altered glial morphology and reduced nascent protein synthesis relative to controls. While TDP-43^{WT} produced a trend towards decreased protein synthesis, TDP-43^{G298S} significantly reduced FUNCAT signal in both the VNC and NMJ. TDP-43 overexpression also altered the spatial distribution of newly synthesized proteins within glial cells, suggesting disruption of compartmentalized translation, transport, or protein degradation. Translational defects at the NMJ indicate these effects may extend beyond central glial cell bodies to distal processes. Consistent with these findings, BONCAT analysis of adult brains revealed reduced levels of newly synthesized proteins in TDP-43^{G298S}-expressing animals, supporting broader impairment of glial translation. Ongoing BONCAT-MS analyses will identify proteins with altered synthesis in TDP-43-expressing glia and uncover molecular mechanisms linking translational dysregulation to ALS pathogenesis. Together, these findings indicate that TDP-43 proteinopathy disrupts glial protein synthesis at subcellular levels and identify translational dysregulation as a potential mechanism contributing to glial dysfunction in ALS.

Disclosures: N.A. Hall: None. **D. de Paula Moreira:** None. **B. Chauhan:** None. **R. Sharma:** None. **B. Lovell:** None. **P. Pirrotte:** None. **D.C. Zarnescu:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.23/Y22

Topic: C.06. Neuromuscular Diseases

Title: Correcting cryptic splicing in a TDP-43 deficient mouse model of ALS

Authors: *A. ANAND[1,2], J. WLASCHIN[3], S. ANTONUCCI[4], P. FRATTA[5], C. E. LE PICHON[6];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and ultimately fatal neurodegenerative disease that affects thousands of patients and their families. 97% of ALS patients display a common pathology where the essential nucleic acid binding protein, TDP-43, is mislocalized outside of neuronal nuclei. Due to its role in RNA splicing, mislocalization of TDP-43, out of the nucleus results in the aberrant splicing of numerous transcripts, including the inclusion of normally repressed cryptic exons. To understand the early changes associated with nuclear loss of TDP-43, we examined the functional and transcriptomic alterations in a mouse model where TDP-43 is conditionally deleted from motor neurons. By compound muscle action potential recordings, we detect a significant reduction in motor neuron function preceding motor neuron loss and muscle denervation. We also observed upregulation of motor neuron stress responses, down regulation of critical ion channel genes, and many other transcriptional alterations associated with TDP-43 loss of function. To determine if restoration of TDP-43's splice repression would be sufficient to restore motor neuron function, we are leveraging precision medicine strategies to specifically target TDP-43 deficient cells for transgene expression. We are currently testing and optimizing multiple approaches to correct aspects of TDP-43 pathology.

Disclosures: A. Anand: None. **J. Wlaschin:** None. **S. Antonucci:** None. **P. Fratta:** None. **C.E. Le Pichon:** None.

Poster

PSTR309: ALS and Motor Neuron Diseases: Human Genetics, Cellular Mechanisms, and Animal Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR309.24/Y23

Topic: C.06. Neuromuscular Diseases

Title: Building Translatable In Vitro and In Vivo Models Linking TDP-43-Driven Pathology to Neuroinflammation in ALS

Authors: *L. J. BOGART[1], M. RILEY[1], M. LABRANCHE[1], F. MAHMUD[1], F. BAHARI[2], M. TWAROG[1], J. HSIAO[1], C. QUIGLEY[1], F. SCORRANO[3], A. MADDEN[1], A. PATEL[1], D. FEUERBACH[4], K. WORRINGER[1], D. R. SHIMSHEK[4];
[1]Neurosci., [2]Comparative Med., Novartis Biomed. Res., Cambridge, MA; [3]Comparative Med., [4]Neurosci., Novartis Biomed. Res., Basel, Switzerland

Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease characterized by the misfolding, mislocalization, and aggregation of proteins, such as TDP-43. PET scan imaging has shown that microglial activation is most pronounced in regions with motor neuron loss and correlates with TDP-43 pathology. Microglia can shift toward a proinflammatory and neurotoxic functional state, negatively impacting the course of progression in neurodegenerative diseases. TREM2 receptor-mediated signaling is critical for neuroprotective microglial functions. Therefore, targeting microglia through TREM2 may help promote reparative microglial function, potentially reducing motor neuron loss and slowing disease progression in ALS patients. We established *in vitro* and *in vivo* models of TDP-43 overexpression (OE) to assess impact of neurodegeneration and microglial responses. We developed a complex human iPSC-derived model involving microglia co-cultured with motor neurons overexpressing TDP-43, delivered via lentivirus (LV). TDP-43 OE resulted in neurodegeneration, as evidenced by an increase in neurofilament light chain (NF-L) correlating with decreased neurite length. These neurodegeneration markers are associated with elevated secretion of the microglial proinflammatory biomarker SPP1 and soluble TREM2 (sTREM2), suggesting engagement of the TREM2 pathway. *In vivo*, a titration of adeno-associated virus (AAV-PHP.eB-*hSYN1-hTARDBP*) was intravenously delivered to drive TDP-43 OE in neurons in wild-type mice. We found increased NF-L in cerebrospinal fluid (CSF) and plasma, which correlated with a rise in SPP1 and sTREM2 levels in CSF. We also observed augmented microgliosis within the spinal cord and a dose-dependent increase in proinflammatory cytokines. Taken together, we identified key features of TDP-43 driven neurotoxicity, dysregulated microglial TREM2 pathway, and associated neuroinflammation, with strong concordance and translatability between our *in vitro* and *in vivo* models. These models will enable mechanistic studies of neuron-microglia crosstalk and serve as valuable tools for evaluating potential interventions targeting the TREM2 pathway to ameliorate neurodegeneration, as well as to support biomarker validation.

Disclosures: L.J. Bogart: A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **M. Riley:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **M. LaBranche:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **F. Mahmud:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **F. Bahari:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **M. Twarog:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **J. Hsiao:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **C. quigley:** A. Employment/Salary (full or part-time):; Novartis AG. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Novartis AG. **F. Scorrano:** A. Employment/Salary (full or part-time):; Novartis

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.01/Y24

Topic: D.03. Stroke

Support: RS-2021-KD000003
RS-2023-00265824
HI20C1234

Title: Proper Candidates for Robot-assisted Gait Training with a Wearable Exoskeleton in Subacute Stroke Patients

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Abstract: Introduction: The overground robot-assisted gait training (RAGT) has been documented to have a positive impact on the recovery of ambulatory function in patients with subacute stroke. The aims of this study was to identify factors associated with the achievement of independent gait after RAGT with an exoskeletal wearable robot in subacute stroke patients. **Methods:** This study was a prespecified analysis of data from a previous international, multicenter, randomized, controlled trial of RAGT compared with the conventional gait training in subacute stroke patients. Each RAGT and the conventional gait training was provided five times per week for a period of four weeks. Gait function was assessed with the Functional ambulatory category (FAC) before and immediately after intervention. An FAC score of >3 immediately post-intervention was defined as the ability to ambulate independently and

clinically significant. Univariate and multivariate binary logistic regression models were used to determine possible predictors of clinically significant response to the RAGT and the conventional gait training. **Results:** We found that the two independent factors with the greatest impact on the response to RAGT for the achievement of independent gait were: 1) initial cognitive function measured with Mini Mental State Examination, and affected lower extremity power measured with lower limb score of Motricity Index ($p<0.05$). However, in the control group, stroke duration from onset to treatment and affected lower extremity power were significant independent factors ($p<0.05$). **Conclusions:** This prespecified analysis suggest that the efficacy of RAGT with a wearable exoskeleton appears to be less dependent on time since onset within the subacute phase, highlighting the importance of preserved cognitive function for optimal outcomes.

Disclosures: W. Chang: None. **T. Kim:** None.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.03/Y26

Topic: D.03. Stroke

Support: American Heart Association

Title: Personalized Contralesional Transcranial Ultrasound Stimulation Improves Paretic Hand Performance in Chronic Stroke: A Proof-of-Principle Study

Authors: *S. BAO, Y.-H. WANG, L. HOU, Y. CHEN, Y. LEI;
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Abstract: Non-invasive neuromodulation frequently targets the contralesional hemisphere to improve post-stroke paretic upper limb function. Transcranial ultrasound stimulation (TUS) offers a novel, high-spatial-resolution approach to precisely modulate localized cortical regions. This within-subject, proof-of-principle study investigated whether personalized, neuronavigated TUS applied to the contralesional primary motor cortex (M1) hand area improves paretic hand performance. Eleven individuals with chronic stroke completed a rapid, submaximal visuomotor pinch force task. Participants underwent randomized, counterbalanced blocks of active TUS and acoustic noise-masked sham, with M1 targets personalized using individual structural MRI and subject-specific computational acoustic simulations. During active TUS, participants demonstrated immediate kinematic improvements compared to sham, characterized by significantly reduced movement duration, greater peak force generation, and a faster time to peak force. Continuous spasticity monitoring revealed no adverse increases in post-session resting muscle tone, and a post-experiment questionnaire verified successful participant blinding. These findings provide compelling proof-of-principle that personalized contralesional TUS can achieve

immediate behavioral facilitation, positioning it as a promising, target-specific tool for stroke neurorehabilitation.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.04/Y27

Topic: D.03. Stroke

Title: Assisting the paretic hand: Targeted NMES during functional grasp training after chronic stroke

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Abstract: Over 50% of the chronic stroke population report impaired use of the affected arm and hand. Rehabilitation of the paretic upper extremity involves activity-based therapies often combined with neuromuscular electrical stimulation (NMES) to improve sensorimotor function. However, for facilitating specific hand movements such as grasping, clinically available NMES systems are constrained by their large electrode size, limited electrode availability, and the time required to identify effective stimulation locations and parameters. To overcome these limitations, we used a novel NMES device with over 70 electrodes to deliver focal, customizable stimulation during repetitive-task training in chronic stroke (≥ 6 months). Here, we report the preliminary results for 5 participants (mean age 56 years, range 34-65) with chronic stroke. Participants first underwent an evaluation period that included a systematic search of electrode locations and stimulation parameters effective for facilitating digit extension and thumb rotation. Participants then completed 6 training sessions in which they practiced a grasp-lift-release cylinder task using volitionally driven NMES assistance. Each session consisted of multiple 3-minute training blocks, with participants instructed to complete as many repetitions as possible within each block. Clinical measures were taken before and after NMES. Preliminary results are reported as median [min-max]. Across the 5 participants, the median number of completed repetitions on the grasp-lift-release cylinder task was 10 [5-13] with a median success rate of 76% [14-100]. Testing before and after NMES revealed an improved performance on the same cylinder task as indicated by a reduction in completion time (-5.09 seconds [(-)72.73-12.33]). A reduction in spasticity was also observed after NMES, as evidenced by a decrease of 1 point [(-)2-1] on the Modified Ashworth Scale. Ongoing analysis of surface EMG and hand kinematics will further elucidate the mechanisms associated with improvements in functional task performance. Lastly, our group is actively combining transcutaneous spinal cord stimulation with

NMES-assisted training which may lead to further meaningful improvement in hand recovery in chronic stroke.

Disclosures: R.P. Henderson: A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **E. Ibroci:** A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **Z. Elias:** A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **D. Letscher:** A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **A. Xavier:** None. **A. Jangam:** A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **C. Maffei:** A. Employment/Salary (full or part-time):; Feinstein Institute for Medical Research. **M.F. Liu:** None. **A. Alfasi:** None. **C. Bouton:** A. Employment/Salary (full or part-time):; Feinstein Institutes for Medical Research.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.05/Y28

Topic: D.03. Stroke

Support: UH3 NS121565

Title: Electrophysiological correlates of upper extremity recovery from electrical cortical stimulation for post-stroke rehabilitation

Authors: *H. CHO[1], A. ROBERT-GONZALEZ[2], M. BAHADORI-NEJAD[3], E. STEPHAN[1], G. FRIEDMAN[1], S. D'SOUZA[4], E. KLEIN[5], A. L. KO[1], B. L. GRANNAN[1], K. E. WEAVER[6], S. C. CRAMER[7], C. T. MORITZ[2], J. A. HERRON[1], J. G. OJEMANN[1];
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Abstract: Stroke is a leading cause of human disability. Many stroke rehabilitation efforts aim to overcome these deficits by promoting neural plasticity to improve post-stroke motor function. Neuromodulation-based interventions have been of particular interest due to their potential to more effectively modulate neural excitability and extend functional improvements beyond what can be gained from physical therapy alone. To supplement ongoing efforts in exploring neuromodulation-based approaches, in this work, we present initial efforts of a phase I clinical study utilizing electrical cortical stimulation to improve post-stroke motor function.
As part of the study, three participants in the chronic stage of stroke were implanted with the investigational Brain Interchange (CorTec GmbH, Freiburg, Germany) and received open-loop, 50 Hz electrical stimulation paired with upper extremity occupational therapy. Two of these participants have completed the entire 6-week rehabilitation regimen. Electrocorticography activity from the ipsilesional cortex was collected while participants performed a reach task with their paretic arm cued by an audible tone. We evaluated changes in the beta (13-30 Hz) event-related desynchronization (ERD) to characterize the potential impact of the combined

stimulation and rehabilitation intervention on neural excitability and its association with clinical function.
Our findings show changes in beta ERD amplitude between pre- and post-intervention states, which vary based upon anatomy. The two participants with evaluable data thus far had a median change in beta ERD at electrode sites within the motor cortex of -12% and -13%, respectively. Observed ERD changes correspond with clinical improvements in the Fugl-Meyer Scale and Wolf Motor Function Test. These preliminary results reinforce the use of ERD as a reliable electrophysiological biomarker for motor planning and execution, and a promising measure of motor function. Furthermore, our outcomes demonstrate the therapeutic potential of electrical cortical stimulation for post-stroke motor recovery.

Disclosures: H. Cho: 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.; Panaxium. **A. Robert-Gonzalez:** None. **M. Bahadori-Nejad:** 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.; Weill Neurohub. **E. Stephan:** None. **G. Friedman:** None. **S. D'Souza:** None. **E. Klein:** None. **A.L. Ko:** None. **B.L. Grannan:** None. **K.E. Weaver:** None. **S.C. Cramer:** F. Consulting Fees (e.g., advisory boards); Panaxium. **C.T. Moritz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Panaxium. **J.A. Herron:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Panaxium. F. Consulting Fees (e.g., advisory boards); Panaxium. **J.G. Ojemann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Panaxium.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.06/Y29

Topic: D.03. Stroke

Support: UH3 NS121565

Title: Direct Cortical Stimulation Enhances Effects of Upper Extremity Rehabilitation and Promotes Long-Lasting Functional Gains After Stroke

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Abstract: After a stroke, two-thirds of individuals present with upper extremity (UE) functional deficits, significantly impacting their independence and quality of life. Traditional UE rehabilitation remains the main treatment approach, but its effects are limited, especially in the chronic phase of stroke. In this study, we combined intense UE rehabilitation with direct cortical stimulation using a novel subdural brain interface to promote neuroplasticity and improve UE function in patients with stroke.

Three participants with significant left-sided UE hemiparesis who had experienced a stroke 2-5 years prior to enrolment were implanted with a CorTec wireless system (CorTec GmbH, Freiburg, Germany). Patient-specific electrode pairs were selected to deliver 50 Hz cortical surface stimulation during the treatment phase of the study. Individuals received intensive UE rehabilitation in combination with cortical surface stimulation 2 hours a day, 5 days a week, for 6 weeks. P1 was explanted and is in the follow-up phase of the study, P2 has completed the treatment phase of the study, and P3 is in the third week of the treatment phase.

Primary outcome measures are Upper Extremity Fugl-Meyer (UEFM; impairment) and Wolf Motor Function Test (WMFT; function). P1 and P2 UEFM scores increased by 11 and 9 points over 6 weeks of cortical surface stimulation combined with rehabilitation, respectively, with parallel improvements in the WMFT. P1 functional gains were maintained 7 months after stimulation. P1 regained the ability to operate large tools, manipulate small nuts and bolts, and cut their food. Similarly, P2 regained control of individual finger movements and recovered their ability to tie their shoes, zip up their jacket, and resume playing the piano. Our preliminary results highlight the potential of this combined cortical surface stimulation and rehabilitation intervention to improve UE function and promote long-term independence and quality of life in individuals with stroke.

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Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Panaxium.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

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Program #/Poster #: PSTR310.07/Y30

Topic: D.03. Stroke

Support: NIH Grant NS121565
Weill Neurohub
Panaxium

Title: Resting-State Phase-Amplitude Coupling Vary Across Sessions of Subdural Cortical Stimulation Plus Rehabilitation in Chronic Stroke Patients

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Abstract: Stroke is a leading cause of disability in the United States, with upper extremity (UE) motor impairment being among the most prevalent contributors. Given limited motor recovery achieved by rehabilitation alone after stroke, plasticity-inducing neuromodulation interventions have gained interest for their potential to enhance functional recovery. Here, we present an electrocorticographic (ECoG) characterization of phase-amplitude coupling (PAC) in two ischemic stroke patients presenting with UE motor deficits. These participants are the first to partake in a clinical trial aiming to assess the feasibility and effects of direct subdural cortical stimulation combined with rehabilitation on enhancing functional motor recovery. The two participants were implanted with the investigational CorTec Brain Interchange, which included two 2×8 subdural ECoG electrode grids capable of both recording and stimulation. Following recovery from implantation, participants completed a warm-up phase without stimulation. They then underwent 6 weeks of open-loop (OL) cortical surface stimulation at 50 Hz over a primary motor cortex (M1) site during daily 2-hour UE rehabilitation sessions. During each session, we recorded 2-4 minutes of resting-state activity while participants remained relaxed and alert. The Modulation Index (ModI) scalar was applied within-electrode to quantify the magnitude of theta (4-8 Hz) / low-gamma (30-70 Hz) and beta (12-30 Hz) / low-gamma coupling. Comparisons

were performed between a 1) warm-up session and the first month post-rehabilitation monitoring session, 2) between the beginning and end of the rehabilitation phase, and 3) before versus after an individual rehabilitation session at the end of the rehabilitation phase. In both participants, one with cortical stroke and one with subcortical stroke, we noted robust beta-gamma PAC at M1 at baseline. In all comparisons, there were ModI increases and decreases on a per-electrode basis both anterior and posterior to the central sulcus. In Participant 1, notable ModI changes were observed at several electrodes surrounding M1 from early and late rehabilitation periods. Interestingly, a similar pattern was observed in Participant 2, although only between the warm-up period and the first monitoring visit. These data do not yet support firm conclusions regarding robust physiological coupling changes associated with therapeutic intracranial stimulation. However, they may begin to shed light, at a systems-level, on the neural basis of the observed functional gains and guide the development of future stimulation-based interventions for severe chronic stroke recovery.

Disclosures: M. Bahadori-Nejad: None. **H. Cho:** None. **A. Robert-Gonzalez:** None. **E. Stephan:** None. **G.N. Friedman:** None. **N. Wohns:** None. **J. Fu:** None. **S. D'Souza:** None. **A.M. Anderson:** None. **A.E. Bunnell:** None. **C.J. Creutzfeldt:** None. **D.L. Tirschwell:** None. **E. Klein:** None. **B.L. Grannan:** None. **A.L. Ko:** None. **K.E. Weaver:** None. **S.C. Cramer:** F. Consulting Fees (e.g., advisory boards); Panaxium. **C.T. Moritz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-inventor on a patent owned by the University of Washington which has been licensed to Panaxium. **J.A. Herron:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-inventor on a patent owned by the University of Washington which has been licensed to Panaxium. F. Consulting Fees (e.g., advisory boards); Panaxium. **J.G. Ojemann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-inventors on a patent owned by the University of Washington which has been licensed to Panaxium.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.08/Y31

Topic: D.03. Stroke

Support: NIH UH3 NS121565
Trainee Funding Provided by Weill Neurohub and Panaxium

Title: Longitudinal Characterization of Resting State Spectral Changes Throughout Cortical Stimulation-Assisted Rehabilitation in Chronic Stroke

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A. L. KO[1], B. L. GRANNAN[10], K. E. WEAVER[4], S. C. CRAMER[11], C. T. MORITZ[5], J. A. HERRON[6], J. G. OJEMANN[7];
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Abstract: Three participants (P1-P3) with chronic stroke were implanted with the CorTec Brain Interchange (CorTec GmbH, Freiburg, Germany) in an ongoing clinical trial (clinicaltrials.gov NCT06506279), marking the first collection of chronic subdural electrocorticography (ECoG) data in this population. Open-loop 50 Hz stimulation was delivered while the participant engaged in occupational therapy for two hours/day, five days/week, for six weeks. In order to examine neurological changes associated with recovery, ECoG data were recorded for all sessions, including a two-minute resting state collected before and after each rehab session, as well as during the pre-rehabilitation period and subsequent monthly monitoring visits.
Resting state neural data were filtered using a fourth-order Butterworth IIR filter before the Fitting Oscillations and One-Over-F (FOOOF) algorithm was applied to the power spectra of each of the 32 channels to extract periodic and aperiodic 1/f components. Peaks were aggregated by power within two frequency bands of interest: beta (12-30 Hz) and gamma (30-80 Hz). Hierarchical clustering of channel peak power via Ward's variance minimization algorithm suggests that electrode proximity to the site of stimulation is positively associated with higher beta peak power throughout visits. Beta peak power increases were observed between pre- and post-rehab measurements for all participants. Furthermore, the aperiodic offset and exponent increased throughout the rehab phase for P2, highlighting broadband increases in low gamma (30-50 Hz) power. These findings are consistent with prior work that has identified correlations between increases in both beta activity and low gamma power with improved clinical metrics of functional recovery after stroke. However, a significant decrease in broadband power was observed for P1 when measured 3.5 weeks after rehabilitation concluded and sustained throughout subsequent monitoring visits, despite stability in clinical arm motor assessment scores. This power reduction has not been observed in the monitoring phase data collected thus far for P2. These initial results demonstrate the potential of longitudinal subdural ECoG monitoring for identification of neural spectral dynamics linked to functional motor recovery.

Disclosures: E.J. Stephan: None. **H. Cho:** None. **A. Robert-Gonzalez:** None. **M. Bahadori-Nejad:** None. **S. D'Souza:** None. **G.N. Friedman:** None. **E. Baird-Daniel:** None. **C.J. Creutzfeldt:** None. **E. Klein:** None. **A.L. Ko:** None. **B.L. Grannan:** None. **K.E. Weaver:** None. **S.C. Cramer:** F. Consulting Fees (e.g., advisory boards); Consults for Panaxium. **C.T. Moritz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on a patent owned by the University of Washington which has been licensed to Panaxium. **J.A. Herron:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on a patent owned by the University of Washington which has been licensed to Panaxium. F. Consulting Fees (e.g., advisory boards); Consults for Panaxium. **J.G. Ojemann:** None.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.09/Y32

Topic: D.03. Stroke

Support: Stanford University School of Medicine
Uehara Memorial Foundation Overseas Research Fellowship

Title: Circadian Rhythm Brain State at the Time of Transplantation Influences Functional Recovery After Human Neural Stem Cell Transplantation in Chronic Stroke

Authors: *Y. MAEDA[1], P. HABIB[2], X. LIANG[3], M. KIM[7], N. JOHNSTON[4], J. KIM[5], T. BLISS[6], G. K. STEINBERG[4];
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Abstract: Neurorestorative therapies for chronic stroke remain limited. Human neural stem cell (hNSC) transplantation has demonstrated safety and feasibility; however, therapeutic efficacy varies and the biological factors underlying treatment responsiveness are poorly understood. We hypothesized that the circadian rhythm state of the brain at the time of transplantation may influence recovery dynamics after stem cell therapy.
To address this, adult male Sprague Dawley rats underwent transient middle cerebral artery occlusion (30 min tMCAO) followed one month later by ipsilesional transplantation of embryonic-derived hNSCs (NR1) or vehicle during either the inactive phase (ZT0-6) or active phase (ZT12-18). T2-weighted MRI was used to assess infarct volumes, and neurological recovery was evaluated longitudinally out to 4 months post-stroke using multimodal behavioral assessments (whisker paw, cylinder, elevated body swing, corner turn, and T-maze tests).
All groups had comparable lesions and neurological deficits prior to transplantation, but vehicle-treated animals showed minimal recovery, regardless of treatment timing, whereas both NR1 groups demonstrated significantly improved recovery compared with vehicle-treated controls ($p<0.001$). Notably, animals receiving NR1 during the active phase exhibited significantly accelerated functional recovery compared with inactive-phase NR1 transplantation during the early post-transplant period (2 weeks post-transplantation, $p<0.01$). Both NR1 groups achieved comparable functional recovery (80-90% of baseline) by 12 weeks post-transplantation.
These findings suggest that brain state at the time of transplantation influences stem cell-mediated recovery. Ongoing spatiotemporal multi-omics analyses aim to identify molecular and cellular features associated with transplantation-responsive brain states and circadian-dependent therapeutic recovery.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.10/Z1

Topic: D.03. Stroke

Support: NINDS R01NS058784 (GKS)

Title: Caloric Restriction Primes the Stroke Brain for Enhanced Neural Stem Cell Therapy

Authors: *V. GUPTA, X. LIANG, M. KIM, Y. MAEDA, T. BLISS, G. K. STEINBERG; Dept. of Neurosurg. and Stanford Stroke Ctr., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Human neural stem cell (hNSC) transplantation represents a promising therapeutic strategy for stroke recovery in early clinical trials, yet efficacy varies widely. Our long-term goal is to enhance therapeutic outcomes. Here we test whether caloric restriction (CR), which we have shown alters ischemic brain metabolism, preconditions the rodent ischemic brain to improve hNSC therapeutic efficacy. Adult male C57BL/6 mice underwent either 3-week CR or ad libitum (AL) feeding prior to 35-minute transient middle cerebral artery occlusion (tMCAO). At 7 days post-stroke, mice received anterior subcortical transplantation of our clinically tested hNSCs (NR1) or vehicle. T2-weighted MRI assessed infarct volumes, while neurological recovery was evaluated longitudinally through 3 months post-transplantation using rotating beam and pellet reach tests. A parallel cohort of CR and AL animals was sacrificed immediately before transplantation to characterize the recipient brain microenvironment. mRNA-seq was performed on the ipsilesional anterior hemisphere, followed by differential gene expression analysis (DESeq2) and enrichment analyses using Gene Ontology and KEGG databases via overrepresentation and Gene Set Enrichment Analysis methods. Although lesion volumes and functional deficits were comparable between groups, NR1 transplantation into CR-preconditioned mice produced significantly greater functional recovery compared to NR1 transplantation into AL-fed mice. Vehicle treatment in either CR or AL conditions produced minimal recovery, indicating that therapeutic benefit requires both CR preconditioning and cell therapy. Transcriptomic analysis revealed that AL-fed stroke mice exhibited robust upregulation of phagocytosis and lysosomal pathways at 7 days post-stroke compared to naïve controls. In contrast, CR significantly attenuated exaggerated phagocytic pathways, lysosomal machinery, and TNF- associated inflammatory genes, compared to AL mice, suggesting a distinct, more stable and less inflammatory microenvironment at the time of transplantation. This study demonstrates that caloric restriction modulates the post-stroke brain environment to enhance neural stem cell therapy efficacy by attenuating phagocytosis and inflammation, thereby creating a more receptive microenvironment for cell transplantation.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.11/Z2

Topic: A.04. Transplantation and Regeneration

Support: AHA -25CDA1450365
NIH - 1 R01 NS119872-01

Title: Stabilizing the Gut Barrier for Brain Health - Sex Specific Behavioral and Proteomic Responses to IESC Secretome After Stroke

Authors: *K. MANI[1], F. SOHRABJI[2], Z. AKBARI[3], K. PICKLE[4];
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Abstract: Background: Ischemic stroke impairs both brain and gut function, and poststroke intestinal injury and inflammation are increasingly recognized as contributors to poor cognitive recovery. Our previous work showed that transplanting intestinal epithelial stem cells from a healthy donor to a stroke host repaired the intestinal epithelium and improved stroke recovery. In this study, we tested whether conditioned media derived from intestinal epithelial stem cell (IESC secretome) can support gut repair and, in turn, improve cognitive and social behavior after stroke in middle aged female and male rats. **Methods:** Middle aged male and female Sprague Dawley rats underwent middle cerebral artery occlusion (MCAo) or sham surgery. Animals received three intraperitoneal injections (4, 24, 48 h after stroke) of sex matched IESC secretome from young rats or basal media. Behavioral outcomes were assessed at 4+ weeks after stroke, using social interaction, novel object recognition, and Barnes maze. Distal ileum was examined by H&E staining (villus length to width ratio, crypt villus organization) and Periodic Acid Schiff staining (goblet cell counts). Serum cytokines were measured with multiplex assays. Secretome from male and female IESC organoids was analyzed by label-free LC-MS/MS followed by pathway analysis. **Results:** Stroke produced villus blunting, reduced villus length to width ratio, goblet cell loss, increased gut permeability, and elevated inflammatory cytokines in the acute phase. In the chronic phase, stroke impaired sociability, recognition memory, and spatial performance in both sexes. IESC secretome treatment reduced villus dysmorphology, and lowered circulating inflammatory markers. In males, secretome treatment resulted in near complete recovery of social and cognitive performance, while in females, the same regimen but did not fully normalize cognitive performance. Proteomic analysis revealed a large shared core of secretome proteins in males and females, with only a small subset differing by sex. However, pathway analysis showed divergence: female secretome activated translational, mitochondrial, DNA repair, and immune inflammatory pathways, including IL-17 linked signaling, whereas male secretome suppressed many of these modules. **Conclusion:** IESC secretome regimen supports gut structural repair and dampens systemic inflammation after stroke, highlighting the gut epithelium and its IESC derived secretome as a promising therapeutic, but its translation into neurobehavioral recovery is modified by biological sex.

Disclosures: K. Mani: None. **F. Sohrabji:** None. **Z. Akbari:** None. **K. Pickle:** None.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

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Program #/Poster #: PSTR310.12/Z3

Topic: D.03. Stroke

Support: MOH-000207
OFYIRG23jan-0031
Duke-NUS-KPFA/2021/0047
MOH-000212

Title: Transcriptional code for circuit integration in the injured brain by transplanted human neurons

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Abstract: Neural transplantation holds the potential to repair damaged neural circuits in neurological diseases. However, it remains unknown how the grafted neurons project axons to and make functional connections with the appropriate targets to repair the damaged circuit at the adult stage. Here, we report that human cortical progenitors, transplanted into the ischemic mouse motor cortex, matured and integrated into cortical and subcortical neural circuits, including the corticospinal tract. Neuronal tracing combined with single-nuclei RNA sequencing revealed the close relationship between the transcription profiles of a cortical neuronal subtype, especially those of axon guidance and synapse assembly, with the specific target projection and synapse organization. Machine learning-based regression further identified the transcriptional codes for the targeted projection and circuit integration to reconstruct the damaged circuits. Our finding opens a promising strategy for treating neurological diseases through promoting regeneration and neural transplantation.

Disclosures: Z. Wang: None. **S. Zhang:** None.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

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SENSHIN Medical Research Foundation, Japan; to YW
The Clinical Research Promotion Foundation; to MH

Title: Domain V fragment of perlecan promotes post-stroke tissue repair through endothelial-to-pericyte-like phenotypic transition

Authors: *F. YOSHINO, K. NAKAMURA, Y. OZAKI, H. HARUYAMA, M. HIDAKA, M. TAKASHIMA, T. KIYOHARA, T. AGO;
Dept. of Med. and Clin. Science, Kyushu Univ., Fukuoka City / Fukuoka Prefecture, Japan

Abstract: Perlecan is a heparan sulfate proteoglycan which bridges laminin and type IV collagen to stabilize the structural and functional network of vascular basement membranes. We have shown that C-terminal domain V (DV) fragment of perlecan regulates pericyte recruitment and maintains the integrity of blood-brain barrier in the acute phase of stroke. In the subacute phase of stroke, platelet-derived growth factor receptor β (PDGFRβ)-expressing pericytes mediate fibrotic tissue repair and promote functional recovery. However, the involvement of perlecan in post-stroke tissue repair in the subacute phase has yet to be elucidated. In this study we aimed to evaluate the role of perlecan with conditional perlecan-deficient mice (*Hspg2*$^{-/-}$-TG [Perlecan KO]), in which perinatal lethality is rescued by the expression of perlecan transgene under the cartilage-specific *Col2a1* promoter. We used *Hspg2*$^{+/-}$-TG [Perlecan hetero KO] mice as control. We performed photothrombotic permanent middle cerebral artery occlusion (pMCAO) in male mice of 10-12 weeks old and compared histological and functional outcomes between the two genotypes. The infarct volumes of Perlecan KO mice were larger on day 14 after pMCAO compared to the control (KO 17.3±2.3%, control 13.3±0.8%, p=0.03). Perlecan KO mice also showed worse neurological deficits in the subacute phase (modified neurological severity score: day 3, KO 9 (8-9) vs. control 7 (6-8), p=0.21; day 7, KO 7 (6-8) vs. control 5 (3-6), p=0.03; day 14, KO 5 (4-7) vs. control 3 (3-4), p<0.01). The post-ischemic increase of CD31-positive endothelial cells (ECs) and PDGFRβ-positive pericytes in the periinfarct area was inhibited in Perlecan KO mice (CD31; KO 1.9±0.4% /periinfarct area vs. control 3.4±0.9%, p=0.04: PDGFRβ; KO 30.6±3.6% /periinfarct area vs. control 51.3±8.6%, p=0.01). Immunofluorescence staining with DV-specific antibody suggested the localization of DV fragment in the infarct core, in contrast to full-length perlecan in the periinfarct area. Isolated murine brain ECs cultured on DV-coated dishes showed higher mRNA expression of pericyte markers and endothelial-mesenchymal transition (EndMT)-associated transcription factors than those on the control collagen type I-coated dishes (mRNA arbitrary unit: *Pdgfrb*; DV 2.01±0.10 vs. control 0.99±0.17, p<0.01 : *Col1a1*; DV 1.70±0.10 vs. control 1.00±0.11, p<0.01 : *Snai1*; DV 1.31±0.14 vs. control 1.00±0.03, p<0.01 : *Snai2*; DV 1.44±0.11 vs. control 1.00±0.03, p<0.01). Together, these findings suggest that perlecan DV fragment promotes tissue repair in the subacute phase of stroke by mediating pericyte-like phenotypic transition through EndMT-like mechanisms.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

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Topic: D.03. Stroke

Support: NIH NINDS 5R01NS093057

Title: Hormonal Dynamics Across the Estrous Cycle and Responses to Optogenetic Stimulation After Stroke in Female Mice

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Abstract: Ischemic stroke disrupts the primary lesion site and connected motor networks, leading to persistent functional impairment. Estrogen, particularly 17β-estradiol (E2), may influence ischemic injury and recovery, but endogenous hormone levels fluctuate across the estrous-cycle and may contribute to variability in response to neuromodulatory interventions. Our previous work showed that excitatory optogenetic stimulation of ipsilesional primary motor cortex (iM1) neurons enhanced plasticity-related markers and improved recovery in male mice. Here, we examined how optogenetic stimulation relates to estrous-cycle dynamics, estrogen exposure, lesion burden, and behavioral recovery in female mice. Female C57BL/6 mice (n=24) underwent AAV1-ChR2 injection and optical fiber implantation in iM1. Five weeks later, mice were subjected to 30-minute transient middle cerebral artery occlusion. Optogenetic stimulation was delivered daily from post-stroke day (PD) 5 to PD14. Estrous stage was monitored by vaginal cytology, and urinary E2 and progesterone were measured by ELISA and normalized to creatinine. Motor function was assessed using the rotating beam test before stroke and on PD4, PD7, PD10, and PD14. Associations among hormone-related measures, infarct size, and behavioral outcomes were evaluated using simple linear regression. Infarct size was quantified histologically, and staining for GFAP, CD68, and MAP2 was used to assess astrocytic activation, microglia/macrophage activation, and neuronal integrity. Post-stroke estrous-cycle patterns differed across mice. Pre-MCAO urinary E2/creatinine was associated with early behavioral deficit (R^2=0.143, p=0.0357), and post-stroke high-estrogen exposure showed a modest relationship with final infarct size, although this association requires further validation. However, this did not translate into a clear relationship with behavioral improvement from PD4 to PD14 (R^2=0.018, p=0.473). Although estrogen-related measures showed associations with early deficit and lesion-related outcomes, they did not independently explain PD14 motor performance after accounting for early behavioral deficit and lesion size in the severe-deficit subgroup. These findings suggest that estrous-cycle and estrogen-related dynamics may be linked to lesion evolution or early post-stroke injury response, while functional recovery during the stimulation window is likely influenced by additional mechanisms. Future studies will examine how E2- and

progesterone-related dynamics relate to PD15 markers of plasticity, synaptic remodeling, and glial responses in peri-infarct and connected motor regions.

Disclosures: H. Ko: None. **T.C. Chiang:** None. **H. Chen:** None. **R. Kopchock:** None. **N. Radit:** None. **M.Y. Cheng:** None. **G.K. Steinberg:** None.

Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.15/Z6

Topic: D.03. Stroke

Support: Grants-in-Aid for Scientific Research (JSPS): (B) 24K02556 to TA and KN; (C) 25K12344 to YW; (C) 26K11974 to KN
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SENSHIN Medical Research Foundation, Japan; to YW
The Clinical Research Promotion Foundation; to MH

Title: Nox4-dependent metabolic regulation of microglia/macrophage phagocytosis during CNS remyelination

Authors: *K. YAMANAKA[1,2], K. NAKAMURA[1], M. TAKASHIMA[1], T. SHIBAHARA[1], T. KIYOHARA[1], Y. WAKISAKA[1], T. AGO[1];
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Abstract: Oligodendrocyte-mediated myelination is essential for neuronal function, and efficient remyelination after demyelinating injury including stroke requires coordinated myelin debris clearance by microglia/macrophages and subsequent differentiation of oligodendrocyte precursor cells (OPCs). Reactive oxygen species (ROS) are important modulators of glial cell function, but their roles may depend on disease phase and cell type. NOX4, a major ROS-producing NADPH oxidase, is expressed in various CNS and immune cells and is upregulated under cell stress. Here, we examined whether NOX4 regulates microglia/macrophage-mediated myelin debris clearance and trophic support for OPCs during remyelination. Male wild-type (WT) and conventional Nox4 knockout (KO) mice (n=4-18/group) received 0.2% cuprizone (CPZ) for 4 weeks, followed by 1-2 weeks of withdrawal. The corpus callosum (CC) was analyzed by immunohistochemistry and qPCR. Locomotor recovery was assessed by blinded beam-walking. Primary microglia, bone marrow-derived macrophages (BMDMs), astrocytes, and OPCs were used for phagocytosis assays, mitochondrial membrane potential analysis, trophic factor expression, and conditioned medium experiments. After 4 weeks of CPZ exposure, demyelination assessed by myelin basic protein (MBP)-positive area in the CC was comparable between WT and KO mice. However, during remyelination after CPZ withdrawal, KO mice showed greater recovery of MBP-positive myelin area (WT 43.8 ± 2.35% vs. Nox4 KO 60.7 ±

2.50%) and better locomotor function. Before overt remyelination, KO mice already showed increased accumulation of IBA1-positive microglia/macrophages in the demyelinated CC (WT 37.9 ± 5.74% vs. Nox4 KO 62.6 ± 3.28%), accompanied by enhanced IBA1-positive/oil red O-positive myelin debris clearance (WT 30.0 ± 3.67% vs. Nox4 KO 47.6 ± 5.34%) and higher expression of trophic factors. This response was associated with suppression of the phagocytosis-induced increase in mitochondrial membrane potential and increased expression of Igf1 and Grn. Conditioned medium from KO macrophages engulfing myelin debris enhanced OPC growth and expression of myelin-associated proteins, whereas Nox4 deletion did not directly enhance autonomous OPC proliferation. These findings suggest that Nox4 negatively regulates sustained myelin debris clearance by microglia/macrophages. By limiting phagocytic and trophic responses, NOX4 may restrain the cellular environment required for OPC-mediated remyelination. Cell-specific modulation of NOX4 signaling in microglia/macrophages may promote repair in CNS disorders with demyelination.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

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Topic: D.03. Stroke

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SENSHIN Medical Research Foundation
The Clinical Research Promotion Foundation
Manpei Suzuki Diabetes Foundation

Title: Pericyte SGLT2 promotes peri-infarct extracellular matrix deposition and vascular remodeling during post-stroke tissue repair

Authors: *K. NAKAMURA[1], Y. OZAKI[2], M. TAKASHIMA[2], S. KIMURA[2], H. HARUYAMA[2], F. YOSHINO[2], M. HIDAKA[2], K. YAMANAKA[2], T. SHIBAHARA[2], T. KIYOHARA[2], Y. WAKISAKA[2], T. AGO[2];
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Abstract: Sodium-glucose cotransporter 2 (SGLT2) is a glucose transporter mainly expressed in renal proximal tubules and is the pharmacological target of SGLT2 inhibitors. In addition to its role in glucose handling, pharmacological studies suggest that SGLT2 activity may contribute to fibrotic remodeling in peripheral organs. We previously found that SGLT2 expression increases

in PDGFRβ-positive pericytes in the peri-infarct area after ischemic stroke. Because pericytes contribute to extracellular matrix (ECM) deposition, vascular remodeling, and tissue repair after stroke, we hypothesized that pericyte SGLT2 promotes peri-infarct fibrosis and repair during the subacute phase. We used pericyte-targeted SGLT2 conditional knockout mice generated by crossing *Pdgfrb-P2A-CreERT2* mice with *Slc5a2*-floxed mice (*Pdgfrb-P2A-CreERT2+/+;Slc5a2fl/fl*; SGLT2 cKO). *Pdgfrb-P2A-CreERT2+/+;Slc5a2+/+* mice were used as controls. Male mice aged 10-12 weeks underwent photothrombotic permanent middle cerebral artery occlusion. Tamoxifen-containing chow was administered from day 4 after stroke to induce *Slc5a2* deletion during the repair phase. Histological and functional outcomes were assessed on day 21. SGLT2 cKO mice showed reduced SGLT2 expression in PDGFRβ-positive cells in the peri-infarct area. Compared with controls, SGLT2 cKO mice showed decreased accumulation of PDGFRβ-positive pericytes (control 18.8±6.4% vs. cKO 13.0±3.5%), accompanied by reduced peri-infarct deposition of fibronectin and collagen type IV alpha 1, suggesting impaired formation of a reparative fibrotic scar. In parallel, CD31-positive endothelial area was reduced (control 9.2±4.8% vs. cKO 6.7±2.1%), indicating attenuated vascular remodeling. These changes were associated with larger residual MAP2-negative area (control 56.9±19.8% vs. cKO 59.3±14.3%). These findings suggest that pericyte SGLT2 promotes subacute post-stroke repair by supporting PDGFRβ-positive pericyte responses and ECM deposition, leading to reparative fibrotic scar formation. SGLT2 may facilitate the acquisition of a matrix-producing, fibroblast-like phenotype in peri-infarct pericytes, thereby supporting vascular remodeling and tissue repair.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.17/Z8

Topic: D.03. Stroke

Support: KHIDI Grant RS-2023-00265165

Title: Repeated intermittent CO_2 preconditioning reduces ischemia-reperfusion injury and blood-brain barrier disruption after transient middle cerebral artery occlusion

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[4]Cardiol., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [5]Neurol., CHA Bundan Med. Center, Sch. of Med. CHA Univ., Seongnam, Korea, Republic of

Abstract: Carbon dioxide (CO_2) is a potent regulator of cerebral blood flow and may exert protective effects when applied before ischemic injury or before reperfusion. In our previous study, acute CO_2 administration as either preconditioning or perconditioning reduced infarct size and preserved neurovascular unit integrity in a rat transient middle cerebral artery occlusion (tMCAO) model. Here, we examined whether repeated intermittent CO_2 exposure could serve as a preconditioning stimulus against ischemia-reperfusion injury. Adult male Wistar rats were exposed to repeated intermittent CO_2 inhalation before tMCAO. CO_2 was administered at 5%, 10%, or 20% for 3 days, twice daily. Each session consisted of three cycles of 5-min CO_2 exposure separated by 10-min periods of room-air breathing. On the following day, rats underwent 90-min tMCAO followed by reperfusion. Neurological deficits were assessed using Garcia, Longa, modified Neurological Severity Scores (mNSS), and balanced beam tests. Evans Blue extravasation was used to evaluate blood-brain barrier disruption, and TTC staining was performed to measure infarct size. Repeated CO_2 preconditioning was well tolerated, with no mortality or technical failure. TTC staining demonstrated significant reductions in infarct size in the 10% and 20% CO_2 groups compared with tMCAO controls ($p=0.0139$ and $p=0.0017$, respectively), whereas the 5% CO_2 group did not show significant protection. In the 20% CO_2+tMCAO group, infarct size was reduced to $5.83 \pm 3.17\%$ compared with $25.28 \pm 2.17\%$ in tMCAO controls. Rats receiving repeated 20% CO_2 preconditioning also showed improved neurological outcomes, including reduced Longa score (1.8 ± 0.45 vs. 3.0 ± 0.0, $p=0.0079$), reduced mNSS (8.8 ± 1.64 vs. 13.8 ± 0.45, $p=0.0079$), and improved performance on the balanced beam test (86.4 ± 33.15 sec vs. 4.6 ± 3.58 sec, $p=0.0079$). Evans Blue imaging further showed decreased blood-brain barrier (BBB) leakage after repeated CO_2 preconditioning. These findings suggest that rats preconditioned with repeated 20% CO_2 exposure reduces BBB disruption, infarct formation, and neurological deficits after tMCAO. Repeated intermittent CO_2 exposure may serve as a feasible neurovascular brain-priming strategy for against ischemic injury. Further studies will examine whether this protection is linked to microvascular reperfusion, no-reflow reduction, and preservation of neurovascular unit integrity.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.18/Z9

Topic: D.03. Stroke

Support: CIRM (California Institute for Regenerative Medicine) CLIN2-12379

Title: Longitudinal Plasma Proteomics Reveals Molecular Responses to NR1 Stem Cell Transplantation in Chronic Stroke

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Abstract: Stroke is a leading cause of chronic disability, and recovery typically occurs within the first weeks to months after injury, with limited spontaneous recovery in the chronic stage (>6 months after stroke onset). Our lab developed NR1 neural stem cells as a potential therapy to promote recovery after chronic stroke. In a phase 1/2a clinical trial, 18 subjects with chronic stroke received NR1 transplantation directly into the brain tissue, with 67% of subjects showing clinically meaningful motor recovery (≥10 Total Fugl-Meyer Motor Score improvement). To gain insight into potential mechanisms of action of NR1 therapy, we performed SomaScan proteomics (covering ~10,000 unique proteins) on the clinical trial plasma samples. The plasma was collected from subjects prior to transplantation, and at six timepoints post-transplantation: day 7, months 1, 2, 3, 6, and 12. A linear mixed-effects model (LMM) was used to estimate proteomic changes at each post-transplantation timepoint relative to pre-transplantation baseline, while accounting for subject age, sex, and baseline protein expression. Preranked Gene Set Enrichment Analysis (GSEA) from the LMM output revealed significant changes (padjusted < 0.05, |NES| > 1) at every post-transplantation timepoint when compared to the pre-transplantation baseline. Post-transplantation samples showed upregulation of fatty acid and amino acid metabolism pathways, as well as chronic downregulation of complement activation. Weighted gene co-expression network analysis (WGCNA), which groups proteins into modules based on shared expression patterns, identified day 7 protein modules associated with lipid metabolism and the unfolded protein response that were correlated with final recovery at one year post-transplantation ($|r| > 0.7$ and $p < 0.05$). Overall, these findings suggest that NR1 treatment induces systemic changes in key metabolic and immune pathways, and that subtle, early differences in the pathway activation may determine the final motor recovery.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

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Topic: D.03. Stroke

Support: NIH grant R01NS058784
CIRM grant CLIN2-12379

German Research Foundation (DFG) grant HA 9566/1-1
Wu Tsai NPIL Pilot MRI grant

Title: Human neural stem cell transplant drives spatiotemporal pericyte and microglial remodeling after chronic stroke: An integrated imaging and spatial multi-omics study

Authors: *P. HABIB[1], S. EWBANK[2], X. LIANG[3], R. T. NORISTANI[3], N. JOHNSTON[3], J. KIM[4], R. AIRAN[2], T. BLISS[3], G. K. STEINBERG[3];
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Abstract: Intraparenchymal human neural stem cell (hNSC) therapy in chronic stroke patients has shown safety and feasibility, yet efficacy varies and the underlying mechanisms of action remain poorly understood. Focal hNSCs-transplants appear to engage distributed circuits beyond the graft site, suggesting network-level effects. Here, we combined multimodal structural and diffusion MRI with spatial multi-omics to decode these mechanisms. Adult male Sprague-Dawley rats with stable chronic post-stroke deficits received ipsilesional striatal transplantation (Tx) of hNSCs or vehicle one month after stroke. hNSC-treated rats began recovering across six behavioral domains at 6 weeks post-Tx ($p < 0.01$), reaching near-baseline performance by 16 weeks ($p < 0.001$), without reduction in infarct volumes or lesion expansion, suggesting a network-level therapeutic effect independent of lesion repair. Chronic stroke produced bilateral reductions in fractional and quantitative anisotropy (FA & QA) across major white matter tracts. NR1 transplantation significantly increased FA in the corpus callosum (CC, $p < 0.001$), anterior commissure ($p = 0.003$), corticospinal tract ($p = 0.008$), and cingulate cortex ($p = 0.012$), tracts spanning interhemispheric, descending motor, and limbic circuits. Bilateral hippocampal fimbria showed time-dependent FA and QA increase ($p < 0.01$), linking white matter integrity to spatial memory recovery in the T-maze.Single-nuclei-RNA-seq and spatial transcriptomics (Chromium, Visium and Xenium, 10X Genomics) of coronal section at the Tx-site revealed a biphasic molecular mechanism. At Day 1 post-Tx, NR1 induced a 3.7-fold increase in pericytes ($p = 0.018$), not neural progenitors, accompanied by Lgals1 (galectin-1), a pericyte-secreted angiogenic factor, and 106 cell cycle pathways co-activated across the corticostriatal axis. By 3 months, a perivascular matrix stabilization signature emerged anchored by Col1a1 (collagen type I), Tnfrsf11b, and Npr1, (padj < 0.05) with no change in cell type proportions. In the CC, NR1 induced a disease-associated microglial (DAM) signature (Spp1, Gpnmb, Trem2) at 3 months, implicating microglia in white matter remodeling.
Collectively, pericyte expansion (day 1), ECM consolidation (3 months), and DAM activation in the CC co-occur with FA recovery across major white matter tracts without changes in neuronal or oligodendrocyte proportions. This gliovascular remodeling offers mechanistic targets for optimizing and a potential framework for patient stratification and DTI-based response monitoring in hNSC therapy for chronic stroke.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: D.03. Stroke

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CMU Neuroscience Program
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Graduate Research Grant from the Office of Sponsored Programs

Title: Multiple genes knockout using CRISPR/Cas9 Converts Primary Rat Astrocytes into Functional Neurons

Authors: *A. POUDEL[1,2,3], M. TREE[1,2], U. HOCHGESCHWENDER[1,2], D. STORY[1,4,3], G. L. DUNBAR, Sr.[1,4,3], J. BAKKE[2], J. ROSSIGNOL[2,3,1];
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Abstract: Ischemic stroke induces hypoxic injury that triggers a complex cascade of neuroinflammatory responses, releasing pro-inflammatory mediators, activation of reactive astrocytes and progressive neuronal loss. While astrocyte reactivity is initially protective, sustained astrogliosis contributes to a non-permissive (glial scar) environment for neuronal survival and regeneration. Recent studies suggest that reactive astrocytes can be directly reprogrammed into functional neurons by modulating signaling pathways: Notch, glycogen synthase kinase-3 beta (GSK-3β), and bone morphogenetic protein (BMP) pathways. In this study, we investigated whether targeted inhibition of these pathways could drive astrocyte-to-neuron conversion using CRISPR/Cas9-mediated gene editing. We knock-out *Psen1*, a critical component of the Notch signaling pathway; *Gsk3b*, a central regulator of the GSK-3β pathway, and *Bmpr1a*, a receptor in the BMP pathway in primary rat astrocytes. Successful gene knock-out was confirmed by Sanger sequencing, validating efficient CRISPR/Cas9-mediated knockout of all three targets. To assess reprogramming, we performed immunocytochemistry (ICC) for neuronal markers. CRISPR/Cas9-treated astrocytes exhibited a significant increase in neuronal marker expression compared to controls ($p = 0.0023$), indicating successful morphological conversion. Functional maturation of the converted cells was evaluated using multi-electrode array (MEA) recordings. Notably, astrocytes subjected to triple-gene knockout exhibited spontaneous electrical activity starting from 18 days lasting until 28 days, demonstrating the functional neuronal properties. This electrophysiological activity suggests that the induced neurons are not only phenotypically but also functionally comparable to native neurons. We further compared astrocytes derived embryonic day 18 (E18) rats. Passage 0 (P0) astrocytes transfected with CRISPR/Cas9 constructs showed a higher degree of neuronal differentiation relative to E18 astrocytes maintained in astrocyte culture conditions. Collectively, these findings demonstrate that simultaneous disruption of *Psen1*, *Bmpr1a,* and *Gsk3b* effectively reprograms

primary rat astrocytes into functional neurons. This approach highlights the therapeutic potential of pathway-targeted gene editing for neural regeneration following ischemic injury, offering a strategy to replenish lost neurons by harnessing endogenous glial cells.

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Poster

PSTR310: Stroke Recovery Approaches: Neuromodulation, Robotics, and Regeneration

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR310.21/Z12

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: the Korea Institute for Robot Industry Advancement (KIRIA-PMS, 2025-06006) ; Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. RS-2025-02273232)

Title: Effects of Wearable Hip Exoskeleton for Gait Training in Stroke Patients

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Abstract: Introduction: A wearable hip exoskeleton is being proposed as a new gait training method for stroke survivors. The aims of this study was to evaluate the efficacy and safety of gait training with a lightweight wearable hip exoskeleton in ambulatory patients with late subacute or chronic stroke. **Methods:** This multicenter randomized controlled trial was conducted across four rehabilitation centers in South Korea. Thirty-four patients with hemiparetic stroke (onset ≥3 months; Functional Ambulatory Category ≥3) were enrolled. Participants were randomized to receive four weeks of overground gait training (10 sessions; 30 minutes/session, 2-5 times/week) using the Angel Suit H10. The robot-assisted gait training group received adaptive bilateral hip flexion/extension torque (gait-assist mode), while the control group utilized a gravity-compensation mode that offset the device's weight without providing intent-based torque. The primary outcome measure was the change in the Six-Minute Walk Test (6MWT). Secondary outcomes included the 10-Meter Walk Test (10MWT), Motricity Index-Lower Limb (MI-LL), Berg Balance Scale (BBS), Korean Modified Barthel Index (K-MBI), and the occurrence of adverse events. **Results:** Repeated-measures analysis showed a significant group-by-time interaction for 6MWT (p=0.048). The Robot-assisted gait training group significantly improved 6MWT distance (199.2 to 228m, p=0.004), whereas the control group did not (204.5 to 210.6m, p=0.316). Between-group change in 6MWT favored the gait-assist group (p=0.013). Both groups

showed significant improvements in MI-LL and BBS ($p<0.05$), with no significant between-group differences. Neither group improved significantly on 10MWT or K-MBI. No serious adverse events occurred. **Conclusion:** Wearable hip exoskeleton-assisted gait training was safe and improved walking endurance in ambulatory patients with late subacute or chronic stroke, supporting its potential to enhance functional mobility after stroke.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.01/Z13

Topic: D.04. Brain Injury and Trauma

Support: Gates Cambridge Scholarship
NIHR Senior Investigator Award
bit.bio LTD

Title: Modelling Cerebral Metabolic Derangements and Rescue in Traumatic Brain Injury using opti-ox Neurons and Astrocytes

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Abstract: Traumatic brain injury (TBI) precipitates a cascade of cerebral metabolic derangements that contribute to secondary brain injury and long-term sequelae such as neurodegeneration. A key biomarker monitored in neurocritical care is the brain lactate/pyruvate ratio (LPR), which, when elevated > 25, is associated with poor patient outcomes. However, the complexity of injury *in vivo* limits mechanistic dissection. Here, we established a scalable *in vitro* platform using optimised inducible overexpression (opti-ox^{TM}), whereby deterministic transcription factor induction rapidly generates NGN2 glutamatergic neurons and S9AB astrocytes. Cells were acutely exposed to rotenone, an inhibitor of electron transport chain (ETC) complex I, which has been shown to be selectively vulnerable following TBI. We combined extracellular metabolite profiling with measurement of oxygen consumption rate (OCR) and proton efflux rate (PER), proxies for oxidative phosphorylation (OXPHOS) and glycolytic flux, respectively. Metabolic characterisation of the induced cells, including OCR:PER ratios and capacity for glucose, L-glutamine, and fatty acid substrate oxidation, demonstrated phenotypes consistent with primary human cells. Rotenone elevated LPR and recapitulated key cerebral metabolic derangements, including increased glucose consumption, conversion of pyruvate to lactate, and glycerol release, consistent with a shift from OXPHOS to glycolysis seen in TBI patients. This effect was attenuated in astrocytes and co-cultures, suggesting increased resilience and metabolic support. Mitochondrial function assays corroborated the effects of rotenone, revealing dose-dependent decreases in basal and maximal respiration, spare respiratory capacity, and ATP-coupled respiration. Time-course experiments were then performed to investigate lactate-pyruvate linearity, a subject of current clinical research posited to reflect mitochondrial dysfunction in patients. Rotenone reproduced linearity and gradient perturbations seen *in vivo*, supporting the hypothesis that this relationship may reflect underlying ETC disruption. Interventions previously posited as promising neuroprotective candidates in TBI were screened, including succinate and the ketone body β-hydroxybutyrate, both of which partially normalised LPR and warrant further investigation as metabolic rescue agents. This human-relevant model of post-TBI metabolic pathophysiology reproduces bedside LPR states and integrates this translational readout with analysis of mitochondrial function, enabling mechanistic interrogation and evaluation of neuroprotection.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.02/Z14

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R15NS139138

Title: Traumatic brain injury rapidly alters BMEC chirality and polarization in the acute post-injury phase

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Abstract: Under normal conditions, endothelial cells exhibit strong clockwise (CW) chirality that is closely associated with the integrity of the microvessel wall barrier. However, it remains largely unknown whether this chirality is preserved under pathological conditions. Brain microvascular endothelial cells (BMECs) play a central role in maintaining blood-brain barrier (BBB) integrity, whereas traumatic brain injury (TBI) often causes neuroinflammation and BBB dysfunction. However, the acute responses of BMEC chirality and polarization following TBI have not been explored. The goal of this study was to determine whether pediatric TBI induces acute alterations in BMEC chirality and polarity and to identify associated molecular changes. Male and female mouse littermates were randomized at postnatal days 20-21 into Sham or TBI groups (n = 20 animals/group; 10 males/10 females). TBI animals underwent the injury procedure, whereas Sham animals received anesthesia without injury. Experimental personnel were blinded to group assignments. BMECs were isolated from injured brain regions in TBI animals or from corresponding regions in Sham controls. One cohort of isolated BMECs was seeded onto in-house-fabricated ring-shaped micropatterns with a 200 μm inner diameter and a 500 μm outer diameter and cultured for 24-48 hours until confluency. High-resolution phase-contrast images were acquired, and chirality was quantified using a custom MATLAB program. BMEC chirality was classified as CW, counterclockwise (CCW) or non-chiral (NC). A second BMEC cohort was used for gene expression analysis. The results showed that BMECs from Sham animals exhibited predominantly CW chirality, whereas BMECs isolated after TBI showed a marked shift toward NC chirality. Quantitatively, the chiral factor decreased from 0.342 in Sham to 0.075 following TBI, demonstrating a robust injury-associated loss of BMEC handedness. This acute change in chirality was accompanied by activation of pro-inflammatory responses and differential expression of genes involved in cytoskeletal remodeling and cellular signaling pathways. These findings identify BMEC chirality and polarization as previously unrecognized features of the acute neurovascular response to pediatric TBI. By linking endothelial handedness to inflammatory and cytoskeletal signaling changes, this study reveals a novel dimension of BBB dysfunction after brain injury. Targeting BMEC chirality, polarization, and associated cytoskeletal pathways may provide new strategies for assessing TBI-induced neurovascular damage and developing therapeutic approaches to preserve BBB integrity in the immature brain.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.03/Z15

Topic: D.04. Brain Injury and Trauma

Support: NIH grant R01

Title: Role of SARM1 in degeneration of long tracts in traumatic brain injury

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Abstract: The selective role of SARM1 in degeneration of long tracts in traumatic brain injury: a pathway-specific approach using CRISPR-based knockout
Traumatic axonal injury (TAI) involves an active molecular program of delayed axonal breakdown, transitioning the pathology from a passive biomechanical event to a molecularly controlled process. While sterile alpha and Toll/Interleukin 1 receptor motif-containing 1 (SARM1) is a known executioner of Wallerian degeneration, the relative contributions of stress-responsive kinases, such as dual leucine zipper kinase (DLK) and leucine zipper kinase (LZK), in chronic, distal CNS degeneration remain poorly understood. This study investigated the molecular drivers of progressive "dying-back" degeneration in the corticospinal tract (CST), a long descending motor pathway with unique metabolic vulnerabilities. We employed a tract-selective CRISPR-Cas9 strategy to delete *Sarm1*, *Dlk/Lzk*, or both specifically in the CST of Cas9 mice using AAV2-retro-gRNA vectors injected into the lumbar spinal cord. Following impact-acceleration TBI (IA-TBI), we utilized Expansion Microscopy (ExM) to physically enlarge mid-thoracic spinal cord tissue by 2.2x, enabling the resolution of small-caliber axons that are typically below the detection threshold of conventional microscopy. Structural integrity was quantified via an axon-to-soma ratio at 14 and 28 days post-injury. IA-TBI induced significant and progressive loss of distal CST axons (~17% at 14d; ~19% at 28d) in control groups. CRISPR-mediated deletion of SARM1 resulted in a robust ~95% attenuation of this axonal loss, providing durable structural preservation through the 28-day chronic time point. Conversely, DLK/LZK deletion yielded only modest, non-significant protection, suggesting these kinases function as injury sensors rather than primary executioners in this context. These findings establish that chronic long-tract degeneration is an active SARM1-dependent process. While DLK/LZK may modulate injury signaling, SARM1 is the dominant, non-redundant executioner, positioning it as a primary therapeutic target for preserving long-term motor connectivity after TBI.

Disclosures: M. Shayesteh Far: None. **T. Ahmed:** None. **A. Alexandris:** None. **V.E. Koliatsos:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR311.04/Z16

Topic: D.04. Brain Injury and Trauma

Support: NIH grant 1R35NS116852-01
NIH grant 5R37NS077908-08

Title: How cytotoxic is cytotoxic edema? Fluorescent protein quenching and cell swelling in neurons and astrocytes

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Abstract: We recently demonstrated that fluorescent protein (FP) quenching is a powerful early biomarker of apoptosis. Because FPs quench when the intracellular environment becomes increasingly perturbed, they provide a non-invasive, real-time readout of neuronal and astrocytic health. FP quenching typically coincides with disruptions to membrane integrity and metabolic regulation, but its relationship to swelling has yet to be determined. Comparing FP quenching dynamics to changes in cell volume could help distinguish transient osmotic stress from progressive, irreversible injury. In this study, we examined how altering extracellular ion composition affects both swelling and FP quenching in organotypic hippocampal slices, in order to determine whether cytotoxic edema need always be truly cytotoxic.

We utilized organotypic hippocampal slice cultures made from wild-type C57BL/6J mice on P6 and incubated *in vitro*. Using two-photon microscopy, slices were imaged with transgenic fluorophores such as: TurboRFP to visualize healthy neurons, GFAP-GFP to visualize healthy astrocytes, GCaMP to visualize calcium dynamics in neurons, and SuperClomeleon to visualize chloride levels in neurons.

Exposing slices to a sodium-free, high-potassium (or High KCl) solution resulted in significant swelling of the neurons. High KCl perfusion also caused widespread FP quenching, but washout of the High KCl solution restored FP-positivity in some neurons. Astrocytes also swelled and quenched under High KCl conditions, and washout appeared to restore more FP-positivity than in neurons. Exposing slices to a sodium-free, high-lactate (K-Lactate) solution resulted in significant swelling and FP quenching in astrocytes, but little to no effect in neurons. Switching from a sodium isethionate solution to a potassium isethionate (K-Ise) solution caused only minor, delayed, reversible quenching in astrocytes but caused more significant, non-reversible quenching in neurons. There was also only minor swelling in astrocytes and no swelling in neurons during K-Ise perfusion. High KCl perfusion also caused large increases in intracellular calcium and chloride, whereas K-Ise perfusion did not.

Overall, altering extracellular ion composition can cause significant changes in cell volume and FP quenching, with the two being tightly linked. However, the exact nature of the relationship between swelling/quenching and cell death requires further examination. In the future, we intend to determine whether swelling is required to commit cells to a cell death pathway, and whether preventing swelling via alterations in extracellular ion compositions can prevent subsequent cell death.

Disclosures: T. Balena: None. **K.J. Staley:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR311.05/Z17

Topic: D.04. Brain Injury and Trauma

Support: 1R01NS104282-01A1

Title: The Immune and Neuroimmune Response to a Traumatic Brain Injury are Sex-Specific and Differentially Respond to MIF/CD74 Antagonism

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Abstract: Traumatic brain injury (TBI) is a major cause of mortality and disability worldwide. TBI is initiated by an insult to the brain, and the subsequent inflammatory response extends beyond the injured brain parenchyma to involve signaling between peripheral immune compartments. This immune response is driven in part by the release of pro-inflammatory cytokines and activation of innate immune pathways. Macrophage migration inhibitory factor (MIF) is among these mediators, and is upregulated following TBI, along with its receptor, invariant chain (CD74). We have previously shown that antagonizing MIF/CD74 signaling inhibits the astrocytic response to TBI. However, only males were examined, and the peripheral and full extent of the central immune response remain uncharacterized. Sex differences in the susceptibility to TBI have been previously identified, and our preliminary studies suggest baseline sex differences in MIF/CD74 signaling. Therefore, the goal of the current study was to test the hypothesis that TBI will induce sex-specific differences in the neuroimmune and peripheral immune response, that are differentially improved by MIF/CD74 antagonism. Age-matched male and female C57BL/6J (WT) mice underwent sham or a mild-to-moderate lateral fluid percussion injury (FPI) model of TBI. Vehicle (Veh) or ISO-1, a MIF antagonist, was administered 30 minutes post-FPI to antagonize MIF/CD74 signaling. Brain, meninges, and spleen were collected one day post-injury for flow cytometric analysis of innate and adaptive immune populations across brain-associated, and peripheral immune compartments.In the brain, male FPI+Veh mice exhibited a higher frequency of $CD45^{high}$ infiltrating immune cells in the ipsilateral hemisphere, compared to female FPI+Veh ($p=0.0404$) and male Sham+Veh ($p=0.0045$). Female FPI+ISO-1 mice showed reduced frequency of $CD45^{high}$ activated macrophages in the ipsilateral hemisphere relative to the contralateral hemisphere ($p=0.0308$).Sex differences were also observed in B cell subsets. In the spleen, females displayed significantly higher frequencies of CLIP+ B cells compared to males across all groups (Sham+Veh $p=0.0212$; FPI+Veh $p=0.0022$; FPI+ISO-1 $p=0.0119$). Similarly, in the meninges, females displayed significantly higher frequencies of CLIP+ B cells compared to males in Sham+Veh ($p=0.0077$) and FPI+ISO-1 groups ($p=0.0337$).These results demonstrate sex-specific neuroimmune and immune responses following TBI. That MIF/CD74 inhibition differentially modulates immune cell infiltration and activation, underscores the need to examine sex-specific therapeutic approaches to TBI.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.06/Z18

Topic: D.04. Brain Injury and Trauma

Support: (NINDS) (R01NS107370 & R01NS121316)
TOP-NT consortium UG3106941
Georgetown University Medical Center - Dean for Research Pilot Award

Title: Peripheral immune cell infiltration, including macrophages and T-cells, contributes to inflammation in models of Traumatic Brain Injury

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Abstract: Background: Chronic inflammation in Traumatic Brain Injury (TBI) is well established, yet interactions between peripheral and central immune reservoirs remain unclear. This study characterizes neuroimmune responses in two TBI models: High-Frequency Head Impact (HFHI) and Controlled Cortical Impact (CCI).
Methods: C57Bl/6 mice either underwent sham/HFHI procedures (30 closed-head impacts, 5/per day for 6-days) or sham/CCI procedures (craniotomy and 1.25mm impact). Optic tracts were analyzed 1 month post HFHI using immunohistochemistry, Digital Spatial Proteomics (DSP), and RNA-Seq. CCI outcomes were assessed via T Maze 14dpi, and immunofluorescence and RT-qPCR at 1 month.
Results: 1 month post-HFHI, we observe increases in Iba1+ microglia (Sham: 52.6±8.5, 1-month: 350.6±60.7, $p< 0.0001$) and F4/80+ macrophages in the optic tract. DSP indicates peripheral lymphocyte signatures, including CD45, CD11b, and CD4. Immunohistochemistry confirms increased CD3+ T cells (Sham: 0 vs 1-month: 173.60 ± 27.76; $p= 0.033$). RT-qPCR of the optic nerve characterizes a Th1/Tc1 T-cell-subtype signature. Following CCI, there are significant deficits in spontaneous alternations in both male and female mice 14dpi (Sham: 81.17 vs All 14dpi: 40.50, $p<0.0001$). At 1 month, there is increased Iba1+ fluorescence (Sham: 52.90 vs 1-month: 130.2, $p=0.0273$) and CD3+ counts (Sham: 0.1111 vs 1-month: 13.00, $p=0.0213$). RNA-Seq further demonstrates T-memory cell-related genes.
Conclusion: Mild repetitive head impacts and CCI both involve the recruitment of peripheral immune cells to the CNS, but potentially via different mechanisms.This understanding could provide insight into mechanisms for treatment for TBI.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01 NS 077541 (JW)
NIH Grant R01 NS 094527 (JW)
NIH Grant R01 NS 145443 (JW)
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Title: Hv1 proton channel is essential for splenic antibacterial defense and immune homeostasis during the chronic phase of traumatic brain injury in male mice

Authors: *Z. LEI[1], R. KHAN[2], Y. LI[1], K. BRUNNER[1], P. DEVLIN[2], R. M. RITZEL[2,1,3], J. WU[1];
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Abstract: Background: Traumatic brain injury (TBI) is increasingly recognized as a chronic condition with lasting systemic consequences. Beyond persistent neuroinflammation, long-term TBI disrupts peripheral immune homeostasis, increasing susceptibility to infection and organ dysfunction, particularly in older patients. The voltage-gated proton channel Hv1, expressed in microglia and peripheral immune cells, regulates oxidative injury via modulation of NADPH oxidase activity. Yet few animal studies extend long enough to recapitulate the lifelong trajectory of human TBI, leaving the long-term effects of Hv1 deficiency on systemic immune homeostasis unresolved.
Methods: Young adult (3-month-old) male wildtype (WT) and Hv1 knockout (Hv1KO) mice were subjected to a moderate controlled cortical impact (CCI), and survival was monitored for up to 18 months post-injury, with endpoint analyses performed at 21 months of age. After neurological behavioral assessments, spleen, lung, liver, gut, ipsilateral cortex, and blood samples were collected for flow cytometry, qPCR, NanoString nCounter Panels, and *in vivo* plasma transfer studies.
Results: Hv1 deficiency resulted in significantly increased mortality following TBI, starting at 14 months post-injury, compared with WT/TBI mice. No significant difference in survival was observed between the two sham groups. At 18 months post-injury, Hv1KO mice exhibited significant weight loss and splenomegaly. qPCR revealed an approximately 30-fold increase of pan-bacterial 16S rRNA levels in the spleens of Hv1KO/TBI mice, but not in the lungs or liver. Furthermore, chronic TBI in the Hv1KO mice led to a compromised intestinal tight junction and

mucus barrier integrity, accompanied by aberrant activation of the cyclic GMP-AMP synthase-stimulator of interferon genes pathway in the spleen. Transcriptomic profiling of the spleen, liver, and lung revealed distinct post-injury immune signatures in Hv1KO mice. In contrast, surviving Hv1KO/TBI mice showed modest behavioral resilience and a partially neuroprotective cortical transcriptomic profile. Lastly, systemic transfer of plasma from WT/TBI or Hv1KO donors into naïve young adult mice altered immune responses in the spleen, lung, and brain. **Conclusions:** Hv1 plays a critical role in maintaining peripheral immune integrity and antibacterial defense throughout the chronic course of TBI. Despite conferring modest neuroprotection through attenuation of microglial-mediated oxidative stress, Hv1 deficiency exacerbated systemic phagocyte dysfunction and significantly reduced long-term survival.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.08/Z20

Topic: D.04. Brain Injury and Trauma

Title: Converging mechanisms of injury: blast neurotrauma alters VEEV-associated neuropathology

Authors: *J. Y. BAKIR[1,2], S. MURPHY[3], M. VANDERGIESSEN[4], B. HEATH[4], K. KEHN-HALL[4], P. J. VANDEVORD[3];
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Abstract: Introduction: Service members face unique occupational hazards, including concurrent exposure to blast-related traumatic brain injury (bTBI) and infectious diseases. Over the past two decades, more than 450,000 TBIs have been reported in the U.S. military, alongside 10,000+ arboviral infections between 2012-2019. Both bTBI and viral encephalitis specifically Venezuelan equine encephalitis virus (VEEV) produce overlapping neurological sequelae, like cognitive impairment, behavioral disorders, headaches, and increased risk of neurodegeneration. However, the extent and drivers of neuropathology following the combined injury remain poorly understood. Given the likelihood of co-exposure, defining the mechanisms underlying this polytrauma is critical. Mitochondrial dysfunction (MD) has emerged as a central contributor to both TBI and VEEV. Therefore, this study establishes the first dual-insult model of bTBI+VEEV to define neuropathologic consequences and potential therapeutic strategies.
Methods: 8 week old male C57BL/6J mice (n= 6-10/group) were assigned into two cohorts pre

infection (PrI): Blast (B) and Sham (S) and post infection (PoI): S Mock(M), S VEEV(V), BM, or BV. Mice received repeated blast overpressure using an Advanced Blast Simulator located at Virginia Tech. Twelve days later, PrI mice were euthanized and PoI animals were intranasally infected with VEEV TC-83 (2.7E7 PFU). Clinical and neurological status were scored daily on a 0-3 scale (normal-severe) for 7 parameters: appearance, mobility, attitude, body condition, altered gait, tremors, and head pressing. Mice were euthanized 7 days post infection (dpi), and brains were collected for mitochondrial isolation. Protein Simple's Jess was used to assess levels of Mitochondrial Fission Factor (MFF) in isolated mitochondria. PrI data were analyzed by t-test and PoI were subject to one-way ANOVA (a=0.05).
Results: SM and BM showed no clinical or neurological deficits, while SV and BV developed symptoms. BV mice exhibited earlier onset compared to SV. Clinical scores were similar between BV and SV, however BV mice were trending for greater mobility deficits at 7dpi ($p = 0.0672$; $F(3, 27) = 37.08$). MFF was elevated in PrI B compared to S.
Conclusions: Though clinical and neurological scores were similar in BV and SV mice, the earlier onset of symptoms in BV points to distinct underlying neuropathology. The shift towards fission in PrI B samples suggests that BV mice are impacted by MD at the point of infection potentiating differences in associated responses to viral exposure. These findings may uncover key drivers and consequences of neuropathologic injury following BV polytrauma.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.09/Z21

Topic: D.04. Brain Injury and Trauma

Support: NIH 1R01NS138259
NIH R01NS142187
EENT Foundation

Title: Elovanoid targets cell transcriptomics, proteomics, mitochondrial functions, synaptic integrity, and counteracts dementia pathology after experimental TBI

Authors: *N. G. BAZAN[1], B. GILES[2], S. BHATTACHARJEE[2], J. JI[2], C. METON DE ALENCAR GADELHA VIEIRA[3], **L. S. BELAYEV**[2];
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability, and there are no effective therapies to protect the brain after an acute brain injury. Recently, we examined the therapeutic efficacy of the homeostatic lipid mediators, elovanoids (ELVs), following TBI in

rats. They promoted functional recovery, preserved hippocampal volume loss, improved regional diffusion metrics in cortical, subcortical, basal ganglia, and limbic regions, and preserved white matter connectivity. The present study examines the cellular and molecular mechanisms underlying ELV's neuroprotective effects at the single-cell level to understand gene regulatory changes that promote synaptic protection and neuronal survival. Sprague-Dawley male young rats (3-4 months old) were subjected to controlled cortical impact (CCI) or a sham model and received intranasal (IN) delivery of ELV-N34 (20 μg) or vehicle at 1h and 24h after CCI. Behavioral scoring, assessed by a composite neurological assessment, was evaluated daily for 3 days. Rats were sacrificed on day 1 to isolate synaptosomes and assess mitochondrial function, and on day 3 to perform single-cell multiome transcriptomic and epigenetic evaluation. Our results suggest that delivery of IN ELV shortly after TBI elicits neuroprotection via synaptic and mitochondrial pathways. Using a single-cell multiome approach, we found an upregulation of genes involved in synaptic integrity. Furthermore, we discovered that ELVs improve synaptosomal mitochondrial function, reduce lipid peroxidation, and increase the activity of antioxidant transcriptional programs, including the NRF2 pathway, in neurons. ELVs reduced CD68-positive inflammatory cell accumulation, decreased 4-HNE-associated lipid peroxidation, and preserved NeuN+ cortical neurons. We suggest that these changes and the induction of cell-type-specific gene regulation in glutamatergic neurons and other cell types underlie ELV-elicited neuroprotection and the counteraction of dementia pathology. Overall, these studies open avenues for the therapeutic use of ELVs.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Topic: D.04. Brain Injury and Trauma

Support: ONR N000142112044
ONR N000142112855

Title: Integrated Cortical Spheroid Model of Primary and Secondary Injury to Delineate Cellular Pathologies in Traumatic Brain Injury

Authors: *M. D. ARAIZA CANIZALES, J. ZHANG, C. FRANCK;
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Abstract: The prevalence of blunt traumatic brain injury (TBI) in the civilian world remains one of the largest public health concerns in the world, accounting for most cases of TBI in the US. Blunt TBI is characterized by its delayed cellular and biological response to mechanical insult, commonly referred to as secondary injury, resulting in a cascade of biochemical processes that

can lead to cell death hours after the initial injury. In contrast, instantaneous cell death post-mechanical load, referred to as primary injury, is less prevalent for civilians but remains a major concern for military personnel exposed to high-pressure shockwaves during deployment or, more commonly, during training exercises. Both blunt and blast TBI exhibit similar injury pathologies, such as astrogliosis, suggesting a similar underlying injury mechanism. However, only blunt TBI consistently showcases patterns of phosphorylation of Tau protein (pTau), a hallmark also observed in other neurodegenerative disorders, such as Alzheimer's disease. Although there is a need to understand both injury mechanisms, existing *in vitro* models are mostly limited to studying secondary injury, while most of the knowledge of primary injury and its biological effects comes from a small number of *in vitro* and *ex vivo* studies. Primary injury requires large strain rates exceeding 200 s^{-1} and reaching into the 1000 s^{-1} range, which are nearly impossible to achieve with traditional apparatus designed to study secondary injury. To address this limitation, we developed a new approach to induce both primary and secondary injury *in vitro* using a single, integrated microfluidic platform to define a quantitative threshold between the two. Utilizing this platform, we apply compression-shear to rat-derived cortical spheroids as they pass through a constriction, where the strain and strain rate are solely determined by the fixed channel geometry and the fluid flow. Cell viability assays performed 1 h and 24 h after injury at two strain rates reveal that samples exposed to 600 s^{-1} showed reduced viability at 24 h, whereas samples injured at 1500 s^{-1} showed immediate cell death. Furthermore, immunostaining of high-rate samples showed immediate damage to microtubules stained for βIII-tubulin, while low-rate samples showed accumulation of pTau 24 h after injury, consistent with secondary injury processes. This novel approach represents the first methodology to controllably and reproducibly induce both primary and secondary injury within the same *in vitro* model.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS R01-NS126247 (ES)
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VA I01BX006921 (ES)

Title: Selective and persistent reduction of parvalbumin-mediated inhibition onto adult-born granule cells after traumatic brain injury

Authors: *C. R. BUTLER[1], C. SQUELLATI[1], E. SCHNELL[2];
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Abstract: The subgranular zone of the hippocampus is one of only two regions in the adult mammalian brain that undergoes adult neurogenesis, and this process is dramatically altered by brain injury. Hippocampal adult neurogenesis is modulated by inhibitory neurotransmitter signaling, and immature adult-born dentate granule cell neurons respond to GABA released from Parvalbumin (PV)-expressing interneurons early in development. Dysfunction and loss of interneurons has been noted in animal models of traumatic brain injury, and thus, changes to PV interneuron function or survival after brain injury could alter the maturation of adult-born neurons and contribute to aberrant post-injury neurogenesis. To investigate this, we used Controlled Cortical Impact (CCI) to model severe brain injury in adult PV-Cre::Channelrhodopsin-2 mice. To label adult-born DGCs, we injected retroviral vectors expressing mCherry into the hippocampus two weeks after sham or CCI injury. Three weeks later, we assessed CCI injury severity using histological measurements and evaluated PV interneurons input onto adult-born DGCs and neighboring mature granule cells using electrophysiological recordings and optogenetics. The density of PV interneurons and the evoked amplitude of PV-mediated inputs onto mature DGCs in CCI-injured mice was unchanged from sham controls. Surprisingly, however, the amplitude of optogenetically evoked PV-mediated inhibitory currents in adult-born DGCs was selectively reduced after CCI. This selective reduction of PV-mediated inhibition onto adult-born DGCs after CCI injury was also observed when granule cells were 6 weeks old, suggesting that this is not related to developmental delay. Our observations highlight a selective and persistent functional change in PV-mediated inhibition onto immature DGCs that are developing within the injured hippocampal circuit. This inability to establish normal inhibitory control of newly born DGCs could contribute to their aberrant network integration and the subsequent development of seizures and post-traumatic epilepsy.

Disclosures: C.R. Butler: None. **C. Squellati:** None. **E. Schnell:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.12/Z24

Topic: D.04. Brain Injury and Trauma

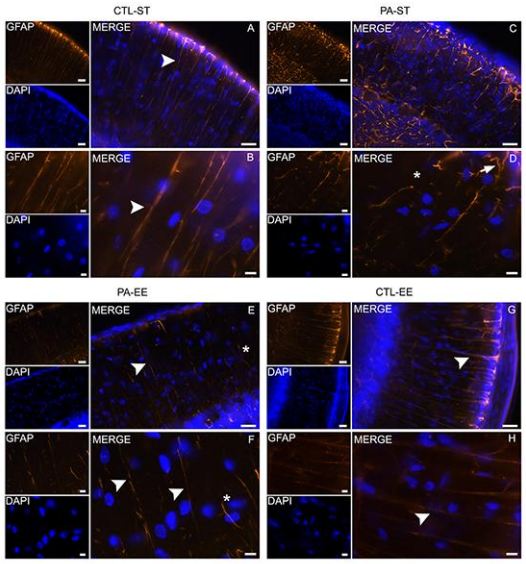
Support: PS1 2026
Fundacion Barcelo 2024

Title: Enriched environment induces astroglial remodeling and functional recovery in the cerebellum after perinatal asphyxia

Authors: M. D'AMBROSIO ANDRADE[1,2], T. KOBIEC[3], P. MARTINEZ CARTIER[4], J. LUACES[3], ***F. CAPANI**[5,6];
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Abstract: Perinatal asphyxia (PA) is a condition caused by insufficient placental gas exchange during pregnancy or labor and is recognized as a leading cause of neonatal brain injury and long-term neurodevelopmental disorders. PA currently has no specific treatment available. In this context, non-pharmacological approaches such as Enriched Environment (EE) have shown promising effects on neuroplasticity and neurological restoration. This study investigated the effects of EE on sensorimotor reflexes and cerebellar morphology in a rat model of PA. Neonatal Sprague Dawley rats were assigned to control (CTL) and PA groups and housed in standard (ST) or enriched (EE) environments until postnatal day 21. Only male pups were included in the study to avoid estrogen related effects. Sensorimotor reflexes were assessed daily and cerebellar tissue was analyzed using GFAP and MAP-2 immunostaining, with GFAP levels additionally quantified by immunoblotting. Regarding sensorimotor reflexes, PA-ST rats exhibited significant deficits in righting ($p < 0.05$), air righting ($p < 0.001$), limb grasp ($p < 0.001$), walking ($p < 0.05$), and negative geotaxis ($p < 0.05$). EE exposure improved or normalized these reflexes, reaching control levels in righting, forelimb grasp and walking reflexes. Additionally, PA-EE group had a shorter walking reflex onset than CTL-ST group. Morphologically, PA-ST rats showed altered Bergmann glia pattern, with fragmented fibers, markedly improved in PA-EE (Fig. 1). Molecular layer thickness was significantly affected by birth condition, with lower mean values observed in PA groups ($p = 0.039$). GFAP reactivity was elevated in CTL-EE and PA-EE groups, with immunoblotting showing a trend toward both birth and housing condition effects, suggesting an early-stage astroglial activation. MAP-2 expression was decreased in PA-ST and PA-EE, with denser labeling near Purkinje cells and lack of reactivity in the distal sector of molecular layer. Together, these findings indicate that EE exposure may contribute to functional improvement and partial cerebellar remodeling following PA.



Disclosures: M. D'Ambrosio Andrade: None. **T. Kobiec:** None. **P. Martinez Cartier:** None. **J. Luaces:** None. **F. Capani:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Topic: D.04. Brain Injury and Trauma

Support: University of Cincinnati Start-Up Funds
NIH (1R21AG085052-01A1)
HJF HU0001-24-2-0102
HU0001-24-2-0075

Title: Modeling CTE-associated pathological features: A human 3D in vitro Triculture system for Mild Repetitive Injury.

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Abstract: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease linked to mild repetitive head trauma. Currently, CTE is definitively diagnosed by postmortem neuropathology of the location of pTAU aggregates, making it impossible to study early disease onset in living patients. Consequently, no diagnostic criteria or targeted treatments exist for individuals with mild repetitive traumatic brain injury (TBI) who may develop CTE. Developing a system to investigate molecular mechanisms and biomarkers throughout the development of CTE is therefore urgently needed. A fully human triculture of iNSC-neurons, primary astrocytes, and HMC3 microglial cells was embedded in 3D silk-collagen scaffolds at a 2:0.5:0.1 million cell ratio, respectively. To establish a robust repetitive injury model, impact conditions—including tip size, speed, and time intervals—were optimized using a controlled cortical impactor (CCI). Our study revealed that calibrated mild impacts (1mm at 1 m/s) maintained neuronal network integrity while enabling robust repetitive injury modeling. Applying three repetitive TBIs with a 14-day interval induced a sustained increase of pTAU (AT8, THR231, PHF1) and TDP-43 up to four weeks after the final injury, confirmed by Western blot, multiplex analysis, and immunofluorescence (Sham: n=5-7, CCI: n=8-12 scaffolds pooled across 2-3 independent experimental sets). Crucially, these injuries triggered significant mitochondrial dysfunction and metabolic shifts. We observed an acute compensatory rise in glycolysis (ECAR) during the first week, followed by a significant glycolytic depression at four weeks. Oxygen consumption (OCR) dropped immediately post-injury, transiently increased by 72 hours, and stabilized by one week. This 3D human model reliably reproduces early CTE-like signatures, demonstrating that a loss of metabolic compensation coincides with sustained proteinopathy. These results position

mitochondrial dysfunction as an early driver of CTE pathology, guiding future studies on metabolic contributors to long-term neurodegeneration.

Disclosures: S. Jun: None. **D. Hinrichsen:** None. **S. Kansakar:** None. **C. Anamala:** None. **M. Thielen:** None. **H. Roberts:** None. **C. Arrasmith:** None. **A.J. Symes:** None. **V. Liaudanskaya:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Program #/Poster #: PSTR311.15/AA2

Topic: D.04. Brain Injury and Trauma

Support: DP1DA06351
K08NS119797
R21HD114071

Title: Conserved Ephrin-Fyn Signaling Links Preterm Hypoxic Brain Injury to Neural Stem Cell Proliferation Deficits

Authors: *P. CHAUHAN[1,5,6], B. RODRIGUEZ[6], T. ROULE[5,2], J. AKOTO[6,5,7], M. SMITH[5,6], E. GADRA[5,6], P. A. DE OLIVEIRA[3], N. AQUIZU LOPEZ[4,2,8], A. CRISTANCHO[4,6,9]; [2]The Raymond G. Perelman Ctr. for Cell. and Mol. Therapeut., [3]Div. of Child Neurol., [4]The Ctr. for Brain Res. in Development, Genetics, and Engin. (BRIDGE), [1]Children's Hosp. of Philadelphia, Philadelphia, PA; [5]The Ctr. for Brain Res. in Development, Genetics, and Engin. (BRIDGE), [6]Div. of Child Neurol., Children's Hosp. of Philadelphia, Philadelphia, PA; [7]Dept. of Pathology, Perelman Sch. of Med. at the Univ. of Pennsylvania, Philadelphia, PA; [8]Dept. of Pathology, [9]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Developmental brain injury is a major risk factor for neurodevelopmental disorders, yet mechanisms linking transient environmental stress to long-term alterations in neural stem and progenitor cells (NSCs/NPCs) behavior remain incompletely defined. Hypoxic brain injury during development is a clinically relevant stressor that disrupts gene regulatory programs in the developing cortex, but how it alters progenitor proliferation dynamics is poorly understood. Here, we investigated whether transient hypoxia reprograms NSC/NPC transcriptional states to impair proliferative capacity. Using a mouse model of transient prenatal hypoxia (5% O_2 at embryonic day 17.5), we identified alterations in cortical NSC cell-cycle programs accompanied by dysregulation of ephrin signaling pathways. These transcriptional changes were associated with reduced thymidine analog incorporation, indicating impaired progenitor proliferation during hypoxic exposure. To determine whether these effects reflect conserved cell-intrinsic mechanisms, we modeled hypoxic stress in human neural progenitor systems, including ReN cells and iPSC-derived NPCs. Both in vitro systems recapitulated hypoxia-induced proliferative deficits observed in vivo, supporting a conserved and largely cell-autonomous response. Cross-

species transcriptomic integration revealed convergent dysregulation of ephrin signaling components and Fyn, a Src-family kinase that modulates Eph receptor signaling and regulates progenitor cell behavior. Ongoing studies are testing whether pharmacologic Fyn inhibition rescues NSCs/NPCs proliferation under hypoxic conditions, providing a potential therapeutic strategy for preterm hypoxic brain injury. Together, these findings identify a conserved ephrin signaling-Fyn kinase axis linking developmental hypoxic stress to impaired NSCs/NPCs proliferation. More broadly, our results demonstrate that transient hypoxia reconfigures transcriptional programs governing neural stem and progenitor cell states, providing a mechanistic framework for how early environmental insults become biologically embedded and shape neurodevelopmental disease susceptibility.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR311.16/AA3

Topic: D.04. Brain Injury and Trauma

Support: ONR Grant GR000037593

Title: Alterations in microglia morphology and expression following an in vitro model of traumatic brain injury

Authors: *E. BLICK[1], B. DEDEKARGINOGLU[2], C. FRANCK[2], A. HAI[1];
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Abstract: Neuroinflammation after traumatic brain injury (TBI) is an underexplored connection between the acute injury and neurodegenerative disease, with post-mortem studies revealing widespread immune activation in the brain up to 18 years post-injury. Microglia, the brain's resident immune cells, play a central role in the aftermath of TBI, as their prolonged activation contributes to dysregulated neuroinflammation, cognitive decline, and neuronal death. Microglia recognize damage-associated molecular patterns (DAMPs) released by injured neurons and rapidly respond through dynamic changes in morphology and function. The microglial response following TBI is, however, not only dictated through biochemical signaling from damaged neurons, but also by the mechanical forces directly experienced by microglia. Despite the increasing recognition of the mechanosensitive nature of microglia, the relationship between specific mechanical parameters and downstream cellular responses remains poorly defined. Most TBI studies are conducted in vivo and, although biologically complex, they preclude reliable application of strain with the accuracy required to determine a correlation between impact and inflammatory response at a single cell level. In this study, we employ a novel, reproducible in

vitro model of TBI to investigate changes in microglial morphology and inflammatory signaling in response to controlled mechanical stress. Microglia are isolated from mixed glial cultures obtained from P0/P1 Sprague Dawley rat cortices and seeded onto a customized dogbone-shaped polydimethylsiloxane (PDMS) substrate. This geometric configuration and substrate composition enable the use of TBI-relevant strain rates without disrupting the gripping points and allow the gauge area hosting the cells to experience a uniform strain field. The dogbone is adhered between two grippers that are contacted by a custom-built tension device to apply programmed uniaxial stress. Strain rates between 1 s -1 to 30 s -1 are evaluated at strains levels of 10 to 50%. Live-cell fluorescence imaging is performed before, during, and after strain application and is analyzed in conjunction with images of fixed samples stained for Iba-1 to examine changes in cell health and morphology. Additionally, relevant proinflammatory cytokines are quantified 24 hours after impact. This approach enables us to investigate the effects of precise, reproducible, and TBI-relevant mechanical strain on microglia. Our findings provide valuable insights into the mechanosensitive response of microglia and could improve our understanding of neuroinflammatory processes following TBI.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.17/AA4

Topic: D.04. Brain Injury and Trauma

Support: DOD Award #: W81XWH-22-2-0056

Title: A time course investigation of microglial inflammation and splenic immune cells following closed head and blast injury

Authors: *M. STEINFELD[1], A. L. RUSSELL[2], A. YENDE[4], A. K. WAGNER[3], A. J. SYMES[5];
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Abstract: Mild Traumatic Brain Injury (mTBI) is among the most prevalent conditions plaguing the general population, with relevance for members of the armed-forces, and can lead to the development of a variety of neuropsychiatric conditions. A potential key mediator of these long-term effects is inflammation in microglia, which assume a pro-inflammatory phenotype after TBI. These neuroimmune responses may play an important role in the long-term sequelae of mTBI, but the exact cellular mechanisms are still unclear. To investigate the role of microglia in TBI, we subjected male C57Bl/6J mice to different combinations of preclinical injury models, including Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA)

and/or advanced blast simulator (ABSI). The CHIMERA model combines direct impact with unrestricted motion to create rapid head acceleration, while blast TBI directs a pressure wave at the animal, simulating an Improvised Explosive Device. To determine the peak time of microglial activation after these injuries, we performed the CHIMERA injury at Day -3, the ABS at Day 0, and isolated Cd11b positive microglia at 1, 3, 7, or 30 days post the second injury (dpi). We then performed qPCR to determine gene expression of several key indicators of inflammation (Cd11b, Il1b, Tnfa, Nlrp3, H2ab1). Concurrently, flow cytometry was performed on splenocytes to characterize the peripheral neuroimmune response. Our results suggest that microglial inflammation is detectable 4 days post CHIMERA, and peaks at 6 days post CHIMERA injury across all markers, regardless of additional exposure to blast. Microglia inflammation returned to baseline by 10 days post CHIMERA. Furthermore, splenocyte analysis reveals a depletion of innate immune cells including macrophages and neutrophils, at 3-6 days post CHIMERA, followed by a later increase in compensatory anti-inflammatory regulatory cells (Tregs). The effect was stronger in CHIMERA-blastTBI combined groups. These findings delineate a distinct, transient therapeutic window for targeting microglial activation post-mTBI and highlight a dynamic central-to-peripheral neuroimmune response that is exacerbated by multi-modal trauma in mice.
Disclaimer:This work is funded by the Congressionally Directed Medical Research Program (Award #: W81XWH-22-2-0056). The opinions and assertions expressed herein are those of the author(s) and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the Department of War or Henry M Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD.

Disclosures: M. Steinfeld: None. **A.L. Russell:** None. **A. Yende:** None. **A.K. Wagner:** None. **A.J. Symes:** None.

Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.18/AA5

Topic: D.04. Brain Injury and Trauma

Support: DOD Military Operational Medicine Research Program Grant, VP-24-006

Title: Synaptic degeneration and early tau phosphorylation following blast exposure in a 3D human triculture model

Authors: *S. GRANT[1], A. YENDE[2], S. JUN[3], V. LIAUDANSKAYA[4], A. J. SYMES[5]; [1]Pharmacol., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]HJF - USUHS, Bethesda, MD; [3]HJF-USUHS, Bethesda, MD; [4]Biomed. Engin., Univ. of Cincinnati, Cincinnati, OH; [5]Pharmacol., Uniformed Services Univ., Silver spring, MD

Abstract: Blast traumatic brain injury (bTBI) is a leading cause of morbidity among military personnel, yet the molecular events linking acute blast exposure to chronic neurodegeneration remain poorly defined. Identifying early pathological sequences in human-relevant systems is critical to developing targeted biomarkers and therapeutic strategies. We employed a 3D in vitro triculture model comprising human induced neural stem cells, astrocytes, and HMC3 microglia grown on silk scaffolds encased in collagen hydrogel to examine the progression of injury following repeated blast exposure. Six-week-old cultures were subjected to two sequential blast exposures at 15-20 psi using an Advanced Blast Simulator and assessed at 1, 3 and 7 days post-injury (DPI). To characterize the injury sequence, we assessed mitochondrial integrity (TOMM20), reactive gliosis (GFAP, vimentin), and structural protein expression (AQP4, APP) across these timepoints. We hypothesize that the acute mitochondrial disruption observed temporally precedes synaptic loss and tau hyperphosphorylation, establishing a mechanistic sequence from bioenergetic failure to early bTBI-relevant pathology in human blast-injured cells. Analysis of this model reveals a biphasic mitochondrial response: TOMM20 decreases acutely at 1 and 3 DPI with recovery by 7 DPI. Interestingly, there is a strong suggestion of astrocyte reactivity, with trending increased expression of both GFAP and Vimentin at 3 DPI by western blot. This suggests that blast has a profound effect on astrocytes in contrast to controlled cortical impact injury. To determine whether the resulting injury sequence of mitochondrial and structural disruption produces downstream synaptic and tau pathology relevant to bTBI, we are characterizing synaptophysin and PSD-95 as markers of pre- and post-synaptic integrity, AT8 phospho-tau (pSer202/Thr205) as an early indicator of potential tauopathy, and SNTF as a soluble index of calpain-mediated axonal damage across all three timepoints. Our results suggest blast exposure produces changes in mitochondrial dynamics, glial reactivity, and structural protein expression in patterns consistent with progressive secondary injury, the downstream synaptic and axonal consequences of which remain under active investigation. This work was funded by the Military Operational Medicine Research Program (MOMRP) to AJS. The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of War.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Program #/Poster #: PSTR311.19/AA6

Topic: D.04. Brain Injury and Trauma

Title: Mild Traumatic Brain Injury Alters Network Dynamics in Aldehyde Dehydrogenase 2 Deficient Primary Neuronal Cultures

Authors: *N. KRISHNAN[1], J. MARTINEZ[5], S. MUFTI[2], C. ADAM[3], J. MILES[3], R. SHI[4], M. CHEN[3];

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Abstract: Aldehyde dehydrogenase 2 deficiency (ALDH2*2) is the most common point mutation in humans, present in approximately 35-45% of East Asians, and increases the risk of developing long-term neurodegeneration. The aldehyde dehydrogenase 2 enzyme (ALDH2) helps clear toxic compounds, one of the most established roles of ALDH2 being in alcohol metabolism in the liver. The ALDH2*2 mutation decreases the enzyme's activity. Our lab has shown that this mutation results in exacerbated damage after spinal cord injury, and other work has shown that having deficient ALDH2 activity increases neuroinflammation after traumatic brain injury (TBI). It is critical to understand the mechanisms by which ALDH2*2 increases susceptibility to neurodegeneration, especially following injury, and it is also important to investigate the role of ALDH2 in mitigating secondary injury damage generally. To this end, we sought to characterize the electrophysiological response of ALDH2*2 neurons to mild impact injury by utilizing our lab's TBI-on-a-Chip model. Primary cortical neurons from mouse embryos were cultured for 3 weeks on microelectrode arrays (MEAs). Recordings were performed under physiological conditions using a miniature incubator chamber. After recording reference activity, cultures were subject to impact injury using the TBI-on-a-Chip pendulum device to administer a single impact of 100g, and post-injury activity was then recorded. Impact injury did not change the average number of firing events per minute, but did alter network dynamics. In particular, interspike intervals, or times between firing events, became more uniform after impact, and the intervals between rhythmic activity decreased. Additionally, cross-correlation analysis revealed changes in firing patterns between signals. Therefore, while average firing rate remained constant, the underlying neuronal dynamics altered after impact. In cultures without the ALDH2*2 mutation, similar changes in interspike intervals and different changes in firing pattern occurred after impact with a higher magnitude force. These changes may indicate altered neuronal communication, as well as an increased susceptibility to impact with the ALDH2*2 mutation. These findings demonstrate the ability of the TBI-on-a-Chip platform and our lab's custom cross correlogram analysis software to reveal subtle but quantifiable changes in network dynamics that are missed by measures like average number of firing events per minute. These findings also demonstrate that the ALDH2*2 mutation might increase susceptibility to long-term neurodegeneration even after mild TBI forces via subtle alterations to neuronal dynamics.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

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Topic: D.04. Brain Injury and Trauma

Support: United States Department of Veterans Affairs Rehabilitation Research and Development Service Merit Review Award # I01 RX003123
United States Department of Veterans Affairs Rehabilitation Research and Development Service Merit Review Award #I01 RX003986-01A1
I. Hermann Anesthesia Foundation Grant AWD #19027

Title: The Noradrenergic Path to Traumatic Brain Injury Recovery

Authors: *K. S. KLIPPEL[1,2], D. PLANT[2], J. HOU[2], F. J. THOMPSON[2], P. K. BOSE[2]; [1]Univ. of Florida, GAINESVILLE, FL; [2]Brain Rehabil. Res. Ctr., North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL

Abstract: Traumatic brain injury (TBI) produces persistent cognitive, affective, and neurobiological dysfunction associated with neuroinflammation, metabolic dysregulation, and disrupted neuronal connectivity. Chronic impairment of noradrenergic (NA) signaling may contribute to prolonged microglial activation, altered energy utilization, and cognitive deficits. We investigated whether chronic methylphenidate (MPH) treatment, a norepinephrine and dopamine reuptake inhibitor, initiated 8 weeks after injury, promotes recovery following experimental mild-moderate closed-head TBI using behavioral testing, FDG-PET, resting-state fMRI, and immunohistochemistry (IHC).Startle-reflex/prepulse inhibition and Morris water maze testing demonstrated restoration of inhibitory gating and improved spatial learning in MPH-treated TBI animals compared with saline-treated TBI controls. MPH-treated TBI animals performed similarly to naïve animals, whereas saline-treated TBI animals exhibited persistent behavioral impairments. FDG-PET revealed elevated hippocampal standardized uptake values (SUVs) in TBI controls at pre- and post-treatment time points, consistent with persistent post-injury hypermetabolism. In the prefrontal cortex and whole brain, TBI controls exhibited elevated SUV, whereas MPH-treated TBI animals demonstrated normalization toward naïve levels, suggesting restoration of metabolic homeostasis. Resting-state fMRI differential chord analyses demonstrated increased hyperconnectivity within anxiety-related circuits in TBI controls over time, whereas MPH-treated TBI animals exhibited reduced hyperconnectivity and reorganization within cognitive networks, consistent with adaptive functional remodeling. Preliminary IHC analyses demonstrated increased activated microglia within multiple ROIs in TBI control animals compared with both naïve and MPH-treated animals, supporting a role for persistent neuroinflammation in chronic injury progression and suggesting that MPH attenuates microglial activation. The convergence of behavioral recovery, normalized glucose metabolism, improved functional connectivity, and reduced microglial activation supports the hypothesis that enhancement of NA signaling mitigates chronic secondary injury processes and facilitates recovery following TBI. Ongoing magnetic resonance spectroscopy and mitochondrial studies will determine whether these improvements are associated with restoration of cellular bioenergetics. These findings demonstrate that NA modulation facilitates recovery from multiple TBI-induced behavioral and cognitive deficits.

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Poster

PSTR311: Brain Injury: Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR311.21/AA8

Topic: D.04. Brain Injury and Trauma

Support: United States Department of Veterans Affairs Rehabilitation Research and Development Service Merit Review Award # I01 RX003123 (B3123–I)
United States Department of Veterans Affairs Rehabilitation Research and Development Service Merit Review Award # I01 RX003986-01A1 (B3986-R)

Title: Traumatic Brain Injury Induces Region-Specific Changes in Noradrenergic Signaling along the Rostrocaudal Axis of the Bed Nucleus of the Stria Terminalis

Authors: *S. TSUDA[1,2], J. HOU[1,2], F. J. THOMPSON[1,3], P. K. BOSE[1,2,4];
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Abstract: Traumatic brain injury (TBI) is a major risk factor for chronic anxiety disorders and post-traumatic stress disorder (PTSD), conditions that substantially impair quality of life and remain difficult to treat. Dysregulation of the noradrenergic (NA) system is strongly implicated in the pathophysiology of anxiety and PTSD, with the bed nucleus of the stria terminalis (BNST) serving as a key limbic hub that regulates sustained fear, stress responsiveness, and anxiety-like behaviors. Because BNST subregions exhibit distinct psychogenic roles along the rostrocaudal axis, identifying region-specific alterations in NA signaling may provide critical insights into the neural mechanisms underlying TBI-associated neuropsychiatric dysfunction. However, the rostrocaudal organization of BNST noradrenergic adaptations following TBI remains unknown. To address this gap, we quantified NA innervation and adrenergic receptor expressions across rostrocaudal BNST subregions following mild-to-moderate closed-head TBI (cTBI) using a standardized weight-drop model. Sixteen weeks following injury, brain tissues of naïve and cTBI rats were coronally sectioned and immunostained for dopamine β-hydroxylase, neuronal nuclei, and various adrenergic receptors. We discovered that NA fiber density in most rostrocaudal subregions of rostral BNST was significantly elevated following cTBI, with higher significance in the rostral-middle, caudal-middle, and caudal anterodorsal BNST (adBNST) subregions as well as the rostral-middle ventrolateral BNST (vlBNST) subregion ($p < 0.001$). In addition, expressions of α2A, α1, and β2 receptors were significantly elevated in most rostrocaudal BNST subregions after injury. Specifically, higher significance was observed for α2A receptor expressions in the rostral/caudal adBNST and vlBNST, α1 receptor expressions in the rostral ventromedial BNST (vmBNST) and vlBNST, and β2 receptor expressions in the caudal vmBNST. These findings demonstrate that chronic cTBI induces robust region-specific remodeling of NA circuitry within the BNST. The differential upregulation of NA innervation and adrenergic receptor expressions across rostrocaudal BNST subregions suggests that TBI disrupts stress- and anxiety-regulating networks in a highly organized manner. Such alterations may contribute to the emergence of persistent anxiety, hyperarousal, and PTSD-like symptoms after TBI. Defining this circuit-level adaptation may facilitate the development of targeted

noradrenergic therapies and biomarker-guided interventions for TBI-associated neuropsychiatric disorders.

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Poster

PSTR312: Brain Injury: Human Studies

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Program #/Poster #: PSTR312.01/AA9

Topic: D.04. Brain Injury and Trauma

Support: MTBI2 MTBI-70-13490
USU- PAT-74-3439.

Title: Traumatic Brain Injury Results in Severe Pathology of the Cerebellar Cortex

Authors: *K. FERRARI[1], M. HUSSAIN[2], D. S. PRIEMER[3], D. PERL[2], S. L. JULIANO[4]; [1]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [3]Pathology, [4]APG, [2]Uniformed Services Univ., Bethesda, MD

Abstract: In recent years, the cerebellum has emerged as an important neural structure controlling many functions in addition to balance and coordination, including cognition, emotion, and sleep. Unfortunately, we know little about the precise effects of traumatic brain injury on the cerebellum. Occupational blast exposure from artillery, explosives, and other weapons is a key characteristic of some military operations that can lead to repeated microtraumas in the brain. To assess the impact of blast related injuries on the human cerebellum, we evaluated the histopathology of warfighters who were either exposed to multiple explosive blasts or control subjects not known to experience such injuries. We obtained human tissue from the DoW/USU Brain Tissue Repository (BTR), consisting of veterans receiving blast injury and control subjects not exposed to occupational blasts. The calbindin immunoreactivity of Purkinje cells and dendritic arbors in blast-injured warfighters were significantly reduced when compared with non-blast injured veterans. When the tissue was immunoreacted against GFAP to reveal Bergmann glia, we uncovered abnormal morphology in the cerebellar cortex, appearing as numerous beaded processes, compared to smooth processes in the control cerebelli. We also examined the white matter of the cerebellum using GFAP and aquaporin 4 (AQP4) immunoreactivity. AQP4 is a water channel protein expressed at the end feet of astroglial cells in many animals, although its expression pattern in the human brain is more extensive. Increases in astrocytic density occurred in the white matter of the cerebellum along with amplified AQP4 immunoreactivity. These data provide evidence that occupational blast exposure can result in severe cerebellar disorganization and likely represent higher level functional involvement, since none of the subjects studied here were known to have motor or coordination deficits.
The authors have no conflicts of interest to report.
The opinions and assertions expressed herein are those of the author(s) and do not reflect the

official policy or position of the Uniformed Services University of the Health Sciences or the Department of War.

Disclosures: K. Ferrari: None. **M. Hussain:** None. **D.S. Priemer:** None. **D. Perl:** None. **S.L. Juliano:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.02/AA10

Topic: D.04. Brain Injury and Trauma

Title: Multilevel longitudinal resting-state EEG reveals evolving neural criticality and delta-band dysconnectivity after mild traumatic brain injury

Authors: *S. PALUDANUS[1,2], P. SKOV-ANDERSEN[3], T. CAHALY[4], R. VAN LUTTERVELD[5];
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Abstract: Background: Resting-state EEG may capture post-injury brain dynamics after mild traumatic brain injury (mTBI), but most studies have been cross-sectional or focused on isolated EEG domains. We used a multilevel longitudinal EEG framework to examine whether early recovery is characterized by changes in oscillatory amplitude, temporal organization, phase synchronization, or network topology. **Methods**: We examined longitudinal resting-state, eyes-closed EEG in individuals with mTBI and healthy controls at 1-15 days, 1.6-3.8 months, and 3.7-5.3 months post-injury. Main analyses included complete cases who passed preprocessing at all sessions (21 mTBI, 15 controls). EEG dynamics were quantified using spectral power, detrended fluctuation analysis (DFA) as an index of neural criticality, phase-lag index (PLI) as a measure of functional connectivity, and minimum spanning tree (MST) diameter as an index of network integration. Longitudinal group differences were tested using nonparametric models with hierarchical follow-up analyses, including electrode-level cluster-based permutation testing. Sensitivity analyses tested robustness to outliers, attrition, epoch count stability, and larger available subsets. **Results**: Whole-brain DFA showed a significant group-specific longitudinal trajectory, increasing over time in the mTBI group while remaining stable in controls. Spatial follow-up analyses indicated that this increase was broadly distributed rather than focal. Delta-band PLI also showed a significant group-specific trajectory: individuals with mTBI had reduced whole-brain delta-band phase synchronization at 1-15 days post-injury, followed by increases over time and convergence toward control levels at later assessments. ROI-pair analyses suggested that this effect was spatially diffuse across inter-regional connections rather than driven by a single pathway. In contrast, spectral power and MST diameter showed no robust

longitudinal group effects. DFA and delta-band PLI were not significantly associated with concurrent post-concussion or depressive symptom scores. **Conclusions**: Early mTBI recovery was characterized by selective longitudinal changes in temporal scaling and delta-band phase synchronization, rather than stable shifts in band power or MST-derived backbone integration. These findings suggest that resting-state EEG recovery after mTBI may be expressed most clearly in the temporal organization and large-scale phase coordination of neural activity, capturing post-injury neurophysiological reorganization not evident from static case-control comparisons or conventional spectral power alone.

Disclosures: S. Paludanus: None. **P. Skov-Andersen:** None. **T. Cahaly:** None. **R. Van Lutterveld:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.03/AA11

Topic: D.04. Brain Injury and Trauma

Support: Funding source: Veterans Affairs Merit Review Award I01 BX004686

Title: Delayed Treatment with a Calcium Release-Activated Calcium (CRAC) Channel Inhibitor Improves Neurological Outcome After Experimental Traumatic Brain Injury in Mice

Authors: R. KACIMI[1], A. MIZUMA[2], M. THIRUPPATHI[1], *J. SHI[3], **M. A. YENARI**[4]; [1]Neurol., San Francisco VA Hlth. Care Syst. and Univ. of California, San Francisco,, San Francisco, CA; [2]Neurol., Tokai Univ. Sch. of Med., Oiso-Machi, Japan; [4]Neurol., [3]Univ. of California San Francisco, San Francisco, CA

Abstract: Delayed Treatment with a Calcium Release-Activated Calcium (CRAC) Channel Inhibitor Improves Neurological Outcome After Experimental Traumatic Brain Injury in Mice Rachid Kacimi [1](presenter), Atsushi Mizuma [1, 2], Manasa Thiruppathi [1], Jian Shi [1](sponsor), Midori Yenari [1]1 Department of Neurology, San Francisco VA Health Care System and University of California, San Francisco, CA 94121 2 Department of Neurology, Tokai University School of Medicine, Kanagawa 259-1193, Japan **Abstract** Inflammation is a hallmark of traumatic brain injury (TBI), and its triggering factors can worsen neurological outcomes. This inflammation is partly driven by microglial activation. Store-operated Ca^{2+} entry through CRAC channels is a key upstream regulator of immune cell activation. CRAC channels are composed of STIM1, an endoplasmic reticulum Ca^{2+} sensor, and Orai1, a plasma membrane pore subunit, which acts via calcineurin. We previously demonstrated that CM5480 (formerly CM-EX-137), a selective small-molecule CRAC channel inhibitor, administered 20 minutes after controlled cortical impact (CCI), reduced lesion size, brain hemorrhage, microglial activation, and sensorimotor deficits in male mice (Mizuma et al., J Neurotrauma 2019). To determine the therapeutic window of CM5480, 32 adult male C57BL/6 mice underwent CCI and received

either CM5480 (5 mg/kg IP) or vehicle. Treatments began 1 hour (n=10/group) or 4 hours (n=6/group) post-CCI, with additional doses given on days 3 and 7. Sensorimotor function was assessed at baseline, and at 7 and 14 days post-CCI, using the elevated body swing, ladder walking, and Rotarod (4-hour cohort only) tests. CM5480 treatment improved running latency on the Rotarod test compared to the vehicle group at individual time points (two-tailed t-test, $p = 0.059$ at day 7, $n = 6$ per group) and showed a significant overall treatment effect across the 14-day recovery period post-TBI (one-way ANOVA, $p = 0.017$). Both delayed treatment groups resulted in significant improvements in body swing and ladder performance compared to the vehicle ($p<0.05$ at days 7 and 14, n=10). Histological assessment of lesion volume and microglial activation is ongoing. These findings indicate that the therapeutic window for selective CRAC channel inhibition extends to at least 4 hours after experimental TBI. This clinically relevant interval is consistent with typical patient presentation times. Therefore, these findings suggest a potential role for clinical use in TBI patients and may warrant investigation at the clinical level. (Funding source: Veterans Affairs Merit Review Award I01 BX004686). Acknowledgements: CalciMedica, Inc provided test compounds.

Disclosures: R. Kacimi: None. **A. Mizuma:** None. **M. Thiruppathi:** None. **J. Shi:** None. **M.A. Yenari:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.04/AA12

Topic: D.04. Brain Injury and Trauma

Support: NIH BRAIN Initiative UH3 NS095554
NIH NINDS R01 NS111019
NIH NINDS R01 NS067249

Title: Thalamo-cortical circuit recruitment in patients with moderate-to-severe traumatic brain injury during therapeutic deep brain stimulation

Authors: *M. P. HOOK[1], N. D. SCHIFF[2], B. K. RUTT[3], J. D. VICTOR[5], J. L. BAKER[8], M. SARANATHAN[9], K. JAMISON[6], A. KUCEYESKI[7], J. M. HENDERSON[4], C. R. BUTSON[10]; [1]Univ. of Florida, Gainesville, FL; [2]Weill Cornell Med., New York, NY; [4]Dept Neurosurgy, R 227, [3]Stanford Univ., Stanford, CA; [5]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [7]Radiology, [6]Weill Cornell Med. Col., Ithaca, NY; [8]BMRI, Cornell University: Weill Cornell Med. Col., New York, NY; [9]Radiology, Univ. of Massachusetts Chan Med. Sch., Worcester, MA; [10]Norman Fixel Inst. for Neurolog. Dis., Fixel Inst., Gainesville, FL

Abstract: Patients with moderate-to-severe traumatic brain injury (msTBI) have major impairments of executive function. The mesocircuit hypothesis posits these deficits stem from downregulation of frontal-striatal regions due to partial deafferentation of its inputs from the

central thalamus. A recent BRAIN Initiative UH3 trial, based on this rationale, demonstrated restoration of executive function in 5 patients following bilateral deep brain stimulation (DBS) of the central lateral (CL) nucleus of thalamus. While the therapy was effective, the precise circuits recruited by central thalamic DBS are unknown. The goal of this work was to identify the circuits recruited by DBS in these patients, by combining structural and stimulation-based whole brain connectivity derived from magnetic resonance imaging (MRI) and biophysical modeling. To do this, we created combined parcellation atlases from the Human Connectome Project atlas, THOMAS atlas, and Freesurfer. Whole brain tractograms were generated with diffusion MRI and MRtrix3 to infer connections between all regions in the parcellation atlas. We then estimated fiber tract activation through patient-specific biophysical models of brain morphology, simulating patient lead location and therapeutic stimulation settings. We found that central thalamus strongly connects to the regions implicated in the mesocircuit hypothesis, and that there is a consistent pattern in how connectivity differs among central thalamic nuclei. Medial nuclei project more strongly to frontal-striatal regions, while lateral nuclei project more strongly to sensorimotor and parietal regions. Our modeling of therapeutic stimulation primarily showed recruitment of frontal-striatal projections from CL and circuits from neighboring thalamic nuclei. Our results indicate that CL stimulation recruits the mesocircuit for improvement in executive function, but that projections from other nuclei including mediodorsal (MD) are also involved.

Disclosures: M.P. Hook: None. **N.D. Schiff:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of ReEmergeDBS. **B.K. Rutt:** None. **J.D. Victor:** None. **J.L. Baker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of ReEmergeDBS. **M. Saranathan:** None. **K. Jamison:** None. **A. Kuceyeski:** None. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of ReEmergeDBS. **C.R. Butson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of ReEmergeDBS.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.05/AA13

Topic: D.04. Brain Injury and Trauma

Title: Goal-Directed Fluid Therapy and Postoperative Airway Parameter in Lateral Position Craniotomy Patients: A Randomized Trial

Authors: *S. DUBE, S. KANDUKURI, H. ROY, G. SINGH;
AIIMS, New Delhi, India

Abstract: Background: Lateral position craniotomy procedures predispose patients to postoperative airway oedema due to positional venous congestion and major intraoperative fluid shifts. We compared the effect of goal-directed fluid therapy (GDFT) vs conventional fluid therapy on postoperative airway parameters in lateral craniotomy patients. **Methods:** After ethical approval and trail registration 40 adults undergoing elective craniotomy in lateral position were enrolled in this prospective, randomized trial. Patients were allocated either to GDFT (Group G) or conventional fluid therapy group (Group C). Ultrasound-measured airway parameters including tongue thickness (TT), oral cavity height (OCH), skin-to-vocal-cord distance (SVT), and skin-to-hyoid distance (SHT) were recorded preoperatively and at 0, 6, 12, and 24 hours postoperatively and compared subsequently. **Results:** Total fluid infused was significantly lower in Group G (p=0.027). Baseline airway parameters were comparable between the groups. SVT was significantly lower in Group G (median 0.890 vs 1.1 cm; p=0.032) immediately after surgery and remained significantly low at all time interval post operatively. TT and SHT were significantly lower in Group G at all four timepoints post operatively. OCH, ventilator duration, ICU stay, and hospital stay did not differ significantly between groups. **Conclusion:** Lateral craniotomy patients receiving GDFT had significantly better airway parameters post operatively. However, this difference did not affect the duration of mechanical ventilation, ICU and hospital stay.

Disclosures: S. Dube: None. **S. Kandukuri:** None. **H. Roy:** None. **G. Singh:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.06/AA14

Topic: D.04. Brain Injury and Trauma

Title: Patterns of Nonconcussive Repetitive Head Impacts in Competitive Soccer: A Comparative Analysis of Youth and Professional Players

Authors: *A. NEVAREZ;
San Diego State Univ., San Diego, CA

Abstract: Title: Patterns of Nonconcussive Repetitive Head Impacts Soccer: A Comparative Analysis of Youth and Professional Players Background: As technology advances in sports, it highlights the increasing number of sports-related concussions(SRC) among athletes of all competitive levels. In the US, approximately3.8 million SRC occur annually, with up to 50% going unreported or undiagnosed. Chronic traumatic encephalopathy (CTE) is a degenerative neurological disease that occurs as a result of repetitive head impacts(RHI), including concussive and nonconcussive hits. Due to increased CTE awareness in athletes who participate in contact sports, there has been an increase in inquiries regarding CTE in soccer players. This study aims to analyze the difference between the rates of RHI from high school and professional players. **Methods:** We analyzed repetitive nonconcussive head impacts

among high school soccer players and Wrexham AFC, a professional soccer team competing in the English Championship League during the 2025- 2026 season. Every head impact sustained during matches was recorded, time-stamped, assigned to the specific player involved, and categorized based on impact type and field position. **Results:** This analysis revealed that head impacts are heavily concentrated among central field positions, which accounted for 78% of all analyzed head impacts. High school soccer matches contained an average of 67 head impacts per game, nearly one impactevery minuteand a half. The results demonstrated trends similar to those observed inboth professionaland highschoolsoccer players, particularly regarding which positions account for the majority of head impacts. However, the professional players averaged approximately 121 headers per match and experienced more severe impacts overall. **Conclusion:** While concussions and CTE have been extensively studied in American football, comparatively little is known about the effects of repetitive head impacts across different levels of soccer participation.

Disclosures: A. Nevarez: None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.07/AA15

Topic: D.04. Brain Injury and Trauma

Title: The Influence of Neurotrauma and Genetic Risk on Network Segregation in an Aging Sample

Authors: *I. PESATI[1], L. BAIRD[2];
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Abstract: Network segregation defines the extent to which a network is connected within itself versus to other networks. Higher segregation indicates that the network is more connected within itself and interacts less with other brain networks, while lower segregation marks greater connectivity to other networks.. This study longitudinally examines the effect between network segregation changes and traumatic brain injury (TBI) status, along with the influence of the APOE4 allele presence, which has been associated with poorer outcomes post-TBI (Crawford, 2002; Sundstrom, 2004).
35 aging adults (nTBI=20, nMale=20, Mage=62.11, SDage=6.89) with and without a history of moderate or severe TBI completed two MRI scans, a health history questionnaire, and a neurocognitive testing session at Pennsylvania State University. APOE4 status was determined using a buccal swab (nAPOE+=19, nAPOE-=16). Graph theory metrics were derived from functional connectivity matrices using scripts from the Brain Connectivity Toolbox.
When global network segregation across the whole brain was cross-sectionally examined using a linear regression analysis, TBI status and positive APOE4 status were not significant predictors

of global segregation (B=4.44e-5, t(30)=0.94, p=0.36). Although they are not predictors at a global level, TBI severity and APOE4 status may predict segregation at the network level. Linear regression analyses were conducted to examine the interaction between TBI status and APOE4 carrier status on the change in network segregation of Default Mode Networks A, B, and C. There was no effect of TBI or APOE4 status on the change in network segregation for any of the default mode subnetworks (Default A: B=2.86e-5, t(30)=0.33, p=0.74; Default B: B=2.27e-5, t(30)=0.30, p=0.77; Default C: B=-4.43e-5, t(30)=-0.54, p=0.59).
We will examine all brain networks defined in the Yeo 17 Network for the Schaefer 400 parcellation to examine more granular effects of TBI and APOE4 status on longitudinal differences in network segregation while controlling for the amount of time between scans (M=714.14, SD=131.47).

Disclosures: I. Pesati: None. **L. Baird:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.08/Web Only

Topic: D.04. Brain Injury and Trauma

Support: Department of Defense Chronic Effects of Neurotrauma Consortium (CENC), Award W81XWH-13-2-0095
Department of Veterans Affairs CENC, Award I01 CX001135
The Resources of the Salisbury VA Healthcare System
National Institute of Health, AA016852
Atrium Health Wake Forest Baptist, Department of Neurology

Title: Multivariate Machine Learning Analysis of M-ECG-derived Heart Rate Variability in TBI Veterans, With and Without Comorbid PTSD

Authors: *A. IZADYSADR[1], H. BAGHERZADEH[2], J. ROWLAND[3,4], S. MARTINDALE[3,4], J. R. STAPLETON-KOTLOSKI[1,2], D. W. GODWIN[1,2];
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Abstract: Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) frequently co-occur in Veterans, producing overlapping symptoms and shared autonomic dysregulation. Heart rate variability (HRV) offers a noninvasive measure of autonomic function. Univariate HRV analyses often fail to capture complex, multivariate patterns associated with comorbidity. This study applied machine learning to HRV features extracted from MEG-derived electrocardiogram (M-ECG) signals to differentiate Veterans with TBI alone (TBI-alone; n = 42) from those with comorbid PTSD (TBI+PTSD; n = 40). Time-domain, frequency-domain, geometric, and

nonlinear HRV metrics were analyzed using nested cross-validated Random Forest and XGBoost classifiers, with Boruta-based feature selection and SHapley Additive exPlanations for model interpretability. Both classifiers achieved above-chance discrimination (Random Forest AUC = 0.663; XGBoost AUC = 0.635). Multivariate models identified distributed autonomic signatures in TBI+PTSD, including altered sympathovagal balance, increased low-frequency proportion, and greater heart rate complexity. In contrast, univariate HRV differences were subtle and did not survive correction for multiple comparisons. These findings demonstrate how using multivariate machine learning HRV analysis could help with detecting comorbidity-specific autonomic patterns, suggesting that HRV-derived signatures may serve as exploratory biomarkers for risk assessment and targeted interventions in Veterans with TBI and PTSD.

Disclosures: A. Izadysadr: None. **H. Bagherzadeh:** None. **J. Rowland:** None. **S. Martindale:** None. **J.R. Stapleton-Kotloski:** None. **D.W. Godwin:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.09/AA16

Topic: D.04. Brain Injury and Trauma

Support: Department of Defense Grant HT9425-23-1-0242
Department of Defense Grant HT9425-25-1-0170

Title: Spreading depolarization recovery phenotypes reveal outcome-linked neurophysiological states after severe traumatic brain injury

Authors: *Z. YIN[1], A. HAYMAN[1], D. CALDWELL[2], X. ZHOU[1], R. PANDA[1], S. NARULA[1], E. HUANG[1], J. YUE[2], R. SIMMONS[1], A. MEFFORD[1], E. AMORIM[1];
[1]Neurol., [2]Neurolog. Surgery, Univ. of California, San Francisco (UCSF), San Francisco, CA

Abstract: Spreading depolarizations (SDs) are ultra-slow waves of electrochemical imbalance that silence electrical activity in neurons and glia after acute severe traumatic brain injury (TBI). SDs occur in at least one-third of patients with severe TBI, yet it remains unclear whether individual SDs reflect the brain's physiological response to trauma or a pathological state contributing to secondary injury. We performed a multidimensional analysis of individual SD events recorded with invasive electrocorticography (ECoG) electrodes placed during the acute phase of severe TBI for seizure monitoring. We analyzed 602 expert-curated SD events from 16 patients with severe TBI (10 died, 6 survived). For each event, trajectories were aligned to SD onset and included the direct-current (DC) amplitude and alternating current (AC) power integral, log broadband power, the aperiodic exponent, and Lempel-Ziv (LZ) complexity. To preserve trajectory shape and cross-signal dynamics, we trained a five-channel 1D convolutional joint variational autoencoder (VAE; input: events x 5 x 1401) with a 16-dimensional latent bottleneck. The joint VAE reconstructed held-out events, with a mean validation R2 of 0.74 +/-

0.02. K-means clustering of the latent event-state space identified three phenotypes with distinct post-SD neurophysiological recovery states. P1 (n=288) showed strong AC suppression (84.5%) without baseline return within 20 min, and a small early-recovery LZ complexity increase (+0.83 z). P2 (n=122) showed milder AC suppression (28.9%) with baseline return within 20 min, and moderate early-recovery LZ complexity increase (+1.11 z). P3 (n=192) showed marked AC suppression (87.8%) with baseline return within 20 min, and the largest early-recovery LZ complexity increase (+1.35 z). In event-level generalized estimating equation (GEE) models adjusting for total SD events and number of electrodes with SD, P2 was enriched among surviving patients (odds ratio [OR]=0.58, p=0.039; 57 survivors and 65 deaths), and P3 was enriched among events from patients who died (OR=2.74, p=0.021; 34 survivors and 158 deaths). Analysis of individual-level temporal evolution showed that survivors had P2 phenotype dominance in the first 48 hours after injury. Patients who died had P3 predominance in the 48-96 h from injury window. Late SD events after 96 h, which occurred mainly in patients who died, shifted toward P1 dominance. This study identified post-SD recovery phenotypes and their timing as critical dimensions of SD neurophysiology after acute severe TBI.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.10/AA17

Topic: D.04. Brain Injury and Trauma

Title: Lesion-Induced Structural Disconnection and Longitudinal ALFF Changes in Traumatic Brain Injury: A Tractography-Based Connectivity Analysis

Authors: *S. NARANG;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Traumatic brain injury disrupts white matter connectivity and alters spontaneous neural activity in structurally connected brain regions, a phenomenon known as diaschisis. Recovery involves widespread functional reorganization, but whether lesion-induced structural disconnection predicts the trajectory of this reorganization, and whether that trajectory differs between patients who develop post-traumatic epilepsy and those who do not, remains poorly understood. We addressed both questions using the TRACK-TBI cohort. First, we quantified structural disconnection severity as the percentage of each brain region's white matter connectivity passing through the lesion, using a two-step tractography pipeline in DSI Studio combining whole-brain fiber tracking with lesion-based filtering using binarized and dilated lesion masks in HCP1065 standard space, applied across 95 patients and 78 bilateral DKT atlas regions of interest, yielding 7,410 subject-region estimates. We correlated this measure with

Amplitude of Low Frequency Fluctuations change from two weeks to six months post-injury in 77 subjects with complete longitudinal fMRI data, using Spearman rank correlations with Benjamini-Hochberg false discovery rate correction across both lesion-masked and non-lesion-masked data. Four regions showed nominally significant associations: right precentral cortex ($r=0.34$, $p=0.002$), right postcentral cortex ($r=0.30$, $p=0.009$), left transverse temporal cortex ($r=0.25$, $p=0.028$), and right pallidum ($r=-0.23$, $p=0.042$). Positive sensorimotor associations are consistent with compensatory upregulation following structural diaschisis, while the pallidum finding suggests a distinct subcortical recovery trajectory. Findings were consistent across masked and non-masked data, confirming effects reflect activity in surrounding tissue rather than lesion signal. Second, we compared longitudinal functional activity change between participants screening positive versus negative for post-traumatic epilepsy to identify functional signatures of epileptogenesis. Together, these analyses characterize both the structural determinants of functional recovery and the network-level changes associated with post-traumatic epilepsy development.

Disclosures: S. Narang: None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.11/AA18

Topic: D.04. Brain Injury and Trauma

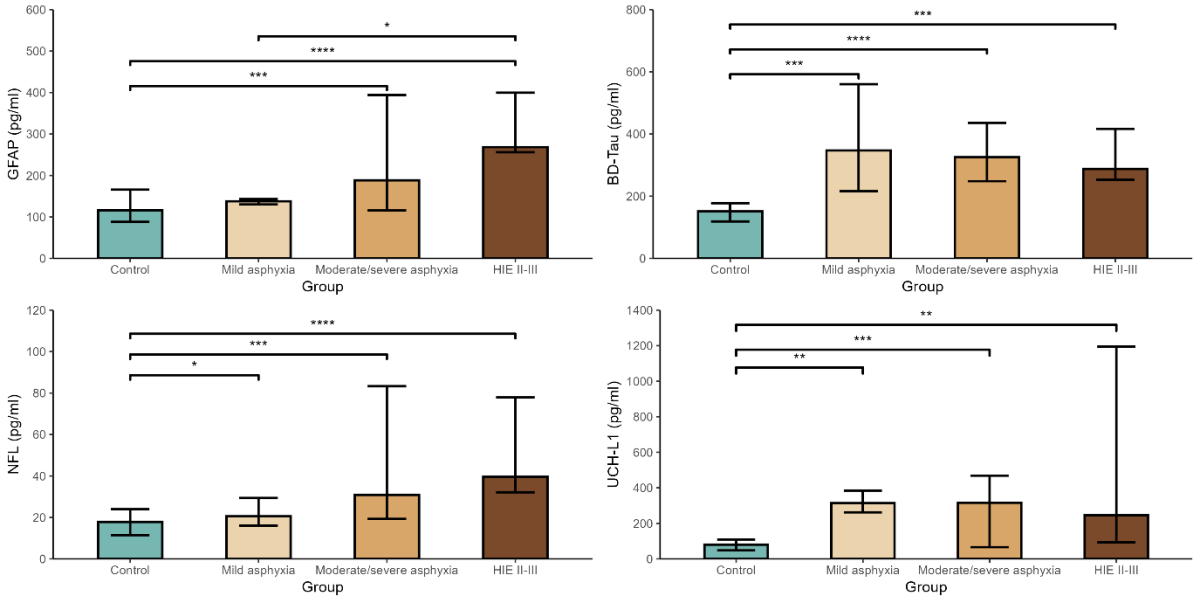
Support: ImmuDocs National Doctoral Education Pilot Based on the Immune System
InFLAMES Flagship Programme of the Academy of Finland
The Sigrid Jusélius Foundation
The Foundation for Pediatric Research

Title: Plasma neuronal injury biomarkers in healthy neonates and infants with perinatal asphyxia

Authors: *K. KORPELA[1,2,3], E. LÖYTTYNIEMI[4], E. SAHA[2,3,5,6], S. RAUTAVA[7], J. KATAJA[8,6], O. PELLONPERÄ[9], B. SINGH[4], V. PARIKKA[2,3,5,6];
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Abstract: Perinatal asphyxia (PA) is caused by impaired respiratory gas exchange, leading to insufficient oxygen delivery to the brain and predisposing newborns to hypoxic-ischaemic encephalopathy (HIE). Early identification and stratification of affected infants remain

challenging and may delay targeted treatment. In this exploratory study, we aimed to determine whether circulating neuronal and glial injury biomarkers measured at birth and within the first 72 h can stratify infants by PA/HIE severity. In addition, we assessed whether mode of delivery affects cord blood biomarker levels. Umbilical cord and peripheral blood samples (0-72 h) were obtained from neonates with PA and healthy controls as part of our prospective follow-up study at Turku University Hospital, Finland. Targeted analyses of brain-derived tau (BD-Tau), neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and ubiquitin c-terminal hydrolase-L1 (UCH-L1) were performed using ultrasensitive single-molecule array assays. Biomarker levels were analysed using linear mixed models including PA/HIE severity and sampling time. A total of 113 infants were included (PA n = 38; controls n = 75). In controls, cord blood BD-Tau, NfL and GFAP means were higher after vaginal delivery than after cesarean section (all $p < 0.0001$). In contrast, most cord blood biomarkers did not differ among controls and severity groups. Postnatally, within 0-7 h, BD-Tau ($p = 0.0082$) and GFAP ($p < 0.0001$) differed among the study groups. After 7 h, NfL also differed by severity ($p = 0.0017$) and increased over the first 72 h in all groups. At 24-48 h, all biomarkers differed among severity groups (all $p < 0.05$) (Fig.). Our findings suggest that BD-Tau, GFAP and NfL can identify infants with PA and distinguish between severity groups, supporting their potential as early biomarkers of brain injury. Their distinct temporal profiles suggest complementary value when used in combination. In healthy infants, cord blood biomarker concentrations were influenced by mode of delivery, which should be accounted for when interpreting cord blood values.



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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.12/AA19

Topic: D.04. Brain Injury and Trauma

Title: The Cognitive Benefits of Creatine Supplementation in a Concussion Population

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Abstract: A traumatic brain injury (TBI) is an acute brain injury that can occur when the head endures an external force. Concussions are a mild form of TBI and affect many individuals every year. While common concussion symptomatology includes headaches, dizziness, and nausea, several other symptoms are less easily identifiable, such as memory impairments, attentional deficits, and mental fatigue. Creatine is a naturally occurring compound that has been shown to have biological benefits, most notably, adenosine triphosphate (ATP) regeneration. In the current study, recruited participants (N = 51) were asked to complete a battery of questionnaires and a computerized cognitive task, the modified paced auditory serial attention task (mPASAT), designed to induce mental fatigue. Self-report scales and eye tracking data (i.e., saccade velocity, pupil diameter, and blink duration) were collected to assess subjective and objective changes in mental fatigue. It was hypothesized that individuals who have previously sustained a concussion would demonstrate greater signs of mental fatigue than those who have not had a concussion. Additionally, it was hypothesized that individuals with a concussion history who are taking creatine would have better performance and reduced mental fatigue on the cognitive task compared to individuals who have had a concussion but are not taking creatine. Multiple repeated measures ANOVAs were computed and found that both objective ($F(1, 46) = 7.048$, $p = .011$) and subjective ($F(1, 46) = 93.581$, $p < .001$) indices of mental fatigue changed over time. Furthermore, mean differences were calculated to assess group differences based on concussion history and current creatine supplementation. Healthy individuals consuming creatine supplements ($M = 4.410$, $SE = 0.490$) reported significantly lower levels of mental fatigue compared to healthy individuals not taking creatine ($M = 5.974$, $SE = 0.490$) with a mean difference of -1.564, 95% CI [0.168, 2.960], $p = .029$. Additionally, individuals with concussion history taking creatine supplements ($M = 5.545$, $SE = 0.568$) reported higher levels of motivation throughout the trials compared to those with concussion history and not taking creatine supplements ($M = 3.667$, $SE = 0.523$) with a mean difference of 1.879, 95% [0.325, 3.433], $p = .019$. Given the limited treatment options currently available for concussions, the results of our study may offer a low-cost and widely accessible treatment option for individuals experiencing concussion-related and general mental fatigue.

Disclosures: T. Adams: None. **V. Morris:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.13/AA20

Topic: D.04. Brain Injury and Trauma

Support: American Society for Laser Medicine & Surgery Grant

Title: Shining a new light into recovery of brain functioning following a mild Traumatic Brain Injury: Using Photobiomodulation therapy to examine cortical functioning differences during n-back task performance

Authors: *H. K. NYARADY[1], D. W. SHUCARD[4], Z. KISH[5], R. O'DONNELL[6], P. ARANY[7], T. MANG[2], J. L. SHUCARD[3], T. J. COVEY[8];
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Abstract: Mild Traumatic Brain Injuries (mTBIs) involve impact to the head that is commonly caused by motor vehicle accidents, sports or recreational activities, work-related injuries, or falling. At injury occurrence, the impact to the head can often result in somatic, cognitive, sensory, and psychological issues. A mTBI can result in disruption of brain functioning and cognitive disturbances. While many patients can often experience a full recovery following a mTBI, other people may experience a longer recovery time, and lingering effects can persist still in many individuals. Effective recovery of brain functioning following mTBI can help individuals return to normal activities, but treatment options remain limited in this population. Photobiomodulation (PBM) is a low-level laser therapy that can be applied directly onto the head and is hypothesized to improve neural functioning and cognitive performance. In a randomized double-blinded feasibility study, we investigated if PBM treatment promotes recovery of brain functioning during cognitive performance following mTBI. Fifteen individuals with a recent mTBI (<3 months) were randomly assigned to either a PBM treatment at 810 nm (n = 8) or sham/control group (n = 7) for six sessions over two weeks. Before and after the intervention, participants completed a computerized N-Back task (testing working memory) while dense electroencephalogram (EEG) recordings were obtained. Event-Related Potentials (ERPs) were derived from the EEG, and the Low-Resolution Electromagnetic Tomography (LORETA) method was applied to estimate cortical activity during task performance. Analyses of variance revealed a significant time (pre, post) X group (PBM, placebo) interaction for the right temporal and right limbic cortex activity during the N1 and P3 ERP component time windows respectively for the 1 back match trials (right temporal at N1: $p = 0.017$, $\eta_p^2 = 0.365$; right limbic at P3: $p = 0.002$, $\eta_p^2 = 0.585$). This interaction was explained by a reduction in cortical activity in the PBM group, in contrast to an increase in cortical activity in the placebo group from pre- to post-treatment. The findings provide preliminary evidence that PBM therapy promoted more efficient cortical activity during working memory processes compared to placebo, potentially reflecting a PBM-induced return to pre-injury functioning.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.14/AA21

Topic: D.04. Brain Injury and Trauma

Support: The Walter L. Copeland Fund of the Pittsburgh Foundation Funding for Cranial Research

Title: Angiogenic & blood brain barrier signaling biomarkers exhibit temporally diverse associations with injury severity and outcome testing following traumatic brain injury

Authors: *J. D. FEDAK[1], S. E. SVIRSKY[2], P. MCINTYRE[2], A. PUCCIO[2], D. OKONKWO[2]; [1]Neurolog. Surgery, Univ. Of Pittsburgh, Pittsburgh, PA, USA, PA; [2]Neurolog. Surgery, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Disruption of the blood brain barrier (BBB) is a secondary injury process leading to neurological deficit after traumatic brain injury (TBI). Matrix metalloproteinase 9 (MMP9), tissue inhibitors of metalloproteinase-1 (TIMP1), vascular endothelial growth factor A (VEGF), interleukin (IL)1β, and tumor necrosis factor alpha (TNFα) play a role in BBB permeability and angiogenesis following TBI. The dynamics of these biomarkers in TBI patients across injury severity and outcome measures have yet to be elucidated in a longitudinal study. We hypothesize that angiogenic signaling and BBB permeability biomarkers will be elevated in subjects with more severe GCS scores and unfavorable GOS-E measurements. Mild (Glasgow Coma Scale (GCS) = 13-15), moderate (GCS = 9-12), and severe (GCS ≤ 8) TBI subjects had blood serum collected 1, 3, 5d, 2w and 12w post-injury and outcome assessments were completed at 2w and 12w. Outcome measurements were dichotomized into favorable (Glasgow Outcome Scale Extended (GOSE) ≥ 5) and unfavorable (GOSE ≤ 4) groups for analysis. Mixed effects models were used to analyze the significance of time, injury severity, and outcome measurements for each biomarker. Time effects were observed for all biomarkers except IL1β when grouped by GCS category or 2/12w GOSE (p<0.005). VEGF showed the only interaction (p=0.013), with a lower concentration in the mild group (m=180.2pg/mL) when compared to severe (m=336.12pg/mL) and moderate (m=250.27pg/mL) subjects at 2w. When grouped by GOSE 2w outcome, TIMP1 and VEGF showed significantly (p=0.019, p=0.043) higher concentrations throughout the time-course in the unfavorable group. VEGF and MMP9 showed time diversity between groups, indicating (p<0.005) elevated concentrations (m=306.3pg/mL, m=2.7e-6pg/mL) at 2w in the unfavorable versus favorable groups (m=138.2pg/mL, m=1.2e-6pg/mL). When grouped by GOSE outcome at 12w the opposite was observed, indicating higher concentrations in the favorable group, with elevated concentrations found throughout the entire time-course in MMP9 (p=0.04) and at 5d in TIMP1 (p=0.03) for the favorable group (m=9.2e-5pg/mL) when compared to the unfavorable group (m=5.1e-5pg/mL). This analysis shows significant time interactions for the measured biomarkers. Specific time-effects were observed for MMP9, TIMP1 and VEGF across multiple groups measured. This may demonstrate a time-sensitive

response of BBB permeability and angiogenesis signaling following injury, the timing of which may determine a neuroprotective or detrimental effect in TBI recovery.

Disclosures: J.D. Fedak: A. Employment/Salary (full or part-time):; University of Pittsburgh, University of Pittsburgh Medical Center (UPMC). **S.E. Svirsky:** A. Employment/Salary (full or part-time):; University of Pittsburgh. **P. McIntyre:** A. Employment/Salary (full or part-time):; University of Pittsburgh. **A. Puccio:** A. Employment/Salary (full or part-time):; University of Pittsburgh. **D. Okonkwo:** A. Employment/Salary (full or part-time):; University of Pittsburgh.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.15/AA22

Topic: D.04. Brain Injury and Trauma

Support: 165646

Title: Deep learning-based hemorrhage volumetry on non-contrast CT: a validated tool for traumatic brain injury research and outcome prediction

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Abstract: Intracranial hemorrhage is a life-threatening complication of traumatic brain injury (TBI) whose clinical management depends critically on accurate, timely volumetric assessment. Manual CT segmentation is time-consuming, subject to inter-reader variability, and not scalable for longitudinal research or multi-site trials. Automated deep learning tools could provide objective hemorrhage quantification in neurotrauma, but no validated solution exists for the low-data, clinically heterogeneous settings typical of TBI research. We developed and validated an automated hemorrhage segmentation system using 48 non-contrast head CT scans from the multicenter PROTECT III trial (FITBIR; mean age 35 years, 73.7% male, 26.3% female; sex differences not assessed), representing the full clinical spectrum of acute TBI hemorrhage (0.5-140 mL). Lesion masks were manually annotated and verified by a board-certified neurosurgeon. The final model (SegResNet-3D) was selected via systematic five-fold cross-validated benchmarking of five architectures under identical preprocessing and evaluation protocols. The validated system achieved mean segmentation Dice of 0.77±0.05 and predicted hemorrhage volume with near-linear accuracy across the full clinical range (R^2=0.970, mean absolute error 4 mL, n=48) — a level of volumetric precision potentially sufficient to support automated hemorrhage burden monitoring in clinical trials. Failure cases were concentrated in thin subdural collections and diffuse multi-compartment bleeds, consistent with the inherent ambiguity of these morphologies on non-contrast CT. To assess real-world generalizability, the system was evaluated on 36 spontaneous intracranial hemorrhage cases (ct-ich dataset), yielding mean Dice

of 0.314±0.354 overall and 0.482±0.335 for lesions exceeding 5 mL (n=22), with performance degradation attributable to scanner resolution and hemorrhage etiology differences — factors clinicians must consider before deploying automated tools across sites. Future work will apply this automated volumetry pipeline to investigate associations between hemorrhage burden, lesion expansion, and functional outcomes in TBI, toward developing imaging-based prognostic tools for neurotrauma clinical trials.

Disclosures: S. Rathi: None. **S. Cheong:** None. **Y. Sham:** None. **U. Samadani:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.16/AA23

Topic: D.04. Brain Injury and Trauma

Support: NIH grant U19AG078109

Title: Analysis of White Matter Hyperintensities, Cognition, and Brain-Iron Quantities in Traumatic Brain Injury

Authors: *A. RODGERS[1,3], H. ZAMANIAN[4], H. WISEMAN[3], B. L. SUSSMAN[3], E. K. DOYLE[5,6], M. BORZAGE[3,2,7];
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Abstract: Background: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide (Yan et al., 2025), and further research is needed to understand how TBI effects white matter health, cognition, and brain iron quantities. We sought to determine how TBI effects white matter hyperintensity (WMH) volume, operational and functional memory, and quantitative iron susceptibility.
Methods: Propensity matched volunteers with and without TBI (N = 65 with, 65 without) underwent analysis for WMH volume and cognitive outcomes. A subset of matched volunteers with available data (N = 39 with TBI, 34 without) had regional iron quantities measured using quantitative susceptibility mapping (QSM). Raw WMH volumes were log transformed and evaluated at multiple time points to assess change over time (Petersen et al., 2025). Cognitive outcomes were measured by the mini mental state examination (Folstein et al., 1975).
Results: Volunteers with TBI had higher ($p = 0.03$) WMH volumes (97.4% higher) than those without TBI. Volunteers with TBI showed a 71.01% more rapid increase in WMH with age compared to matched controls ($m = 0.0761$ vs. $m = 0.0445$, $p < 0.001$). Volunteers both with and without TBI had a positive linear association ($p < 0.05$) between age and log WMH. Volunteers with TBI experienced significantly higher ($p < 0.05$) gaps in memory (118.7% higher) and

current rate of memory decline (68.4 % higher) compared to matched controls. WMH had a significantly positive linear association ($p < 0.05$) with subjective memory complaints, but not with gaps in memory or current rate of memory decline. QSM analysis revealed volunteers with TBI had a nearly significant lower ($p = 0.06$, Cohen's $d = 0.53$) median iron composition in the left internal globus pallidus compared to matched controls. QSM in the right putamen, right striatum, left thalamus and left caudate predicts the current rate of memory decline, as analyzed using linear regression models.
Discussion and Conclusion: As they age, volunteers with TBI experience a 71.01% faster WMH accumulation compared to matched controls. Volunteers with TBI may be more susceptible to effects associated with WMH accumulation and age, such as cognitive decline and memory loss (Habes et al., 2016). QSM was predictive of more cognitive outcome variables in linear regression models compared to WMH, suggesting that QSM is a useful predictor of cognitive outcomes in volunteers with and without TBI. These results identify patterns of WMH accumulation, cognitive outcomes, and iron fluctuation in volunteers with TBI. They warrant additional investigation of regional WMH volumes and QSM in cortical brain matter.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.17/AA24

Topic: D.04. Brain Injury and Trauma

Title: Combining Scalp and Subdural Electrophysiological Recordings to Predict Outcomes in Traumatic Brain Injury Patients

Authors: *M. UDEOZOR[1], L. B. NGWENYA[2], I. BASU[2];
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Abstract: The most common cause of death for patients with severe traumatic brain injury (TBI) is being withdrawn from life-sustaining therapies, removing the possibility for recovery. This underscores the prognostic uncertainty in TBI and demands innovative approaches to leverage TBI-related biomarkers. Recent advances in our understanding of TBI-related pathology (e.g., radiological and laboratory findings) have improved clinicians' ability to diagnose and treat patients; however, capitalizing on these clinical factors to predict long-term recovery remains a challenge. In this retrospective cohort study, we investigated whether acute-phase quantitative electroencephalographic (qEEG) features derived from scalp EEG and electrocorticography (ECoG) can effectively predict long-term outcome. We collected concurrent scalp-EEG and ECoG recordings from 33 post-surgical TBI patients. We measured the relative spectral power across all channels for four canonical frequency bands: delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-30Hz). Using the Glasgow Outcome Scale (GOS) three to six months post-

discharge, we dichotomized patients into poor (GOS 1-3, n = 16) and good (GOS 4-5, n = 17) outcome groups for machine-learning classification. Following a repeated holdout cross-validation procedure, we trained a binary logistic regression (LR) on 80% of the patients and tested it on the remaining 20% over 1000 random splits. Separate models were designed containing features from different frequency bands, as well as a combination of them. Each model was evaluated by its area under the receiver operating characteristic (AUROC) curve. The beta-power model achieved the highest average performance across testing sets (AUROC = 0.704). Interestingly, this outperformed the combined model (AUROC = 0.559), suggesting some features may introduce noise or be anticorrelated. Overall, our preliminary results demonstrate that spectral qEEG features from scalp EEG and ECoG can be leveraged to predict TBI patient outcomes. Future work utilizing non-linear classifiers, such as tree-based models, support vector machines, or neural networks, may improve classification by capturing multi-band dependencies.

Disclosures: M. Udeozor: None. **L.B. Ngwenya:** None. **I. Basu:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.18/AA25

Topic: D.04. Brain Injury and Trauma

Support: DOD Grant HMJF HU0001-24-2-0102/ SUB 1098601-6556
University of Cincinnati Liaudanskaya Start-up Fund

Title: Injury Severity Drives Calcium-Dependent Calpain Activation and Axonal Pathology in a Human 3D Brain Triculture Model

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Abstract: Traumatic brain injury (TBI) leads to long-term neurological disability, yet the human-specific secondary molecular pathways that degrade axonal integrity remain poorly understood. Calpains, calcium-activated proteases central to this process, are difficult to target therapeutically, mainly because existing models do not fully capture the complexity of the injured human brain. To address this gap, we developed a human 3D triculture TBI platform to explore injury severity-dependent relationships between calpain activation, cytoskeletal degradation, and rescue by acetyl-calpastatin.Human induced neural stem cell (iNSC)-derived neurons, primary astrocytes, and HMC3 microglia were embedded in silk-collagen scaffolds and matured over six weeks before being subjected to controlled cortical impact (CCI). Moderate

CCI prompted significant calpain-1/2 activation, peaking at 24 hours, with protease activity up to three times higher than in mild repetitive injury or sham conditions ($p<0.001$). This was accompanied by increased cleavage of α-II-spectrin, PTEN, and APP, along with a graded loss of MAP2 and β3-tubulin ($p<0.01$), consistent with severity-dependent axonal and dendritic degeneration characteristic of calpain-mediated cytoskeletal proteolysis. Continuous acetyl-calpastatin treatment preserved cytoskeletal integrity across different time points and restored cellular architecture close to sham levels.To investigate what drives calpain activation, we engineered a neuronal line expressing GCaMP6s via lentiviral transduction to enable real-time visualization of intracellular calcium dynamics which is the primary trigger of calpain activation. In 2D cultures, these neurons confirmed progressive maturation of spontaneous calcium transients over 4 weeks, validating reporter fidelity and functional readiness. When integrated into the 3D triculture model, these neurons showed increasingly organized calcium dynamics and network activity by week 6, supporting functional integration within the multicellular environment. Future studies will validate our model with bicuculline, AP5, and tetrodotoxin to confirm network functionality. Overall, these findings will help establish a human 3D TBI platform to directly map injury-driven calcium surges to the onset and magnitude of calpain activation, establishing a causal link between post-traumatic calcium dysregulation, downstream cytoskeletal proteolysis, and axonal damage, while also providing a useful tool for testing calpain-targeted therapies.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.19/AA26

Topic: D.04. Brain Injury and Trauma

Support: NIH R01NS121040

Title: Hemodynamic Response Function Subtype Redistribution Following Mild Traumatic Brain Injury

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Abstract: Mild traumatic brain injury (mTBI) is associated with persistent alterations in neurovascular coupling, yet robust imaging biomarkers that capture regionally specific cerebrovascular dysfunction remain limited. Here, we introduce a hemodynamic response function (HRF) subtype-based framework to quantify task-evoked regional neurovascular abnormalities using a multisensory integration paradigm during 3T fMRI. Within 36 predefined

cortical regions of interest (ROIs), event-averaged HRFs were estimated at the voxel level and classified into one of three response subtypes based on a priori shape criteria: positive HRF (pHRF), characterized by a positive peak followed by return to baseline or undershoot; transient-negative HRF (T-nHRF), characterized by an initial negative response followed by a significant positive peak; and fully-developed-negative HRF (FD-nHRF), characterized by a sustained negative response without a subsequent positive peak. Within each ROI, voxel-wise HRFs of each subtype were averaged to generate subtype-specific representative HRFs. A healthy-young control cohort (N=10) defined normative distributions of subtype composition and subtype-specific HRF features, against which mTBI deviations were quantified. mTBI participants (N=10) were examined at a sub-acute stage (<2 weeks post-injury) and a chronic stage (~3 months post-injury) compared with the reference cohort. At the sub-acute stage, a widespread reduction in pHRF prevalence was observed across multiple cortical systems, including auditory, visual, somatomotor, and frontoparietal networks. This was accompanied by a significant increase in T-nHRF across nearly all large-scale functional networks, including default mode and salience networks. In contrast, FD-nHRF expression remained comparatively stable, with limited regional deviations. At the chronic stage, these alterations were markedly attenuated, with substantial normalization of subtype distributions and reduction in T-nHRF predominance. These findings demonstrate that mTBI induces a time-dependent reorganization of task-evoked HRF subtype architecture, characterized by an acute shift from canonical positive responses toward transient-negative responses, followed by partial normalization during recovery. This study therefore showed that HRF subtype composition provides a sensitive and spatially resolved neuroimaging marker of cerebrovascular dysfunction following mTBI, with potential utility for tracking injury evolution and recovery trajectories.

Disclosures: N. J. Fesharaki: None. **A. Vinogradov:** None. **H. Choi:** None. **J. Kim:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.20/AA27

Topic: D.04. Brain Injury and Trauma

Support: NRF_ RS-2025-00520396
NRF_ RS-2025-25396823
NRF_ RS-2025-25396990

Title: Exploring the Neurological Impact of Microplastic Exposure: Insights into TBI, Gut-Brain Axis, and CTRP9's Neuroprotective Role

Authors: *M. PARK[1], H. YANG[3], S. WOO[4], H. JEONG[5], B. CHOI[2], S. SUH[6];
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Abstract: Microplastics, known for their tiny size, are a growing concern in health sciences due to their ability to penetrate the intestinal barrier. This penetration can lead to chronic inflammation, contributing to various gastrointestinal disorders. Moreover, these particles can disrupt gut microbiota, vital for digestive health, immune function, and mental well-being. Our study focuses on the impact of microplastics on Paneth cells in the small intestine, key in maintaining intestinal health and body defense against microbes. These cells are crucial for zinc homeostasis in the gut, influencing antimicrobial pathways. Our research also explores the implications of microplastics on Traumatic Brain Injury (TBI), a severe condition caused by physical head trauma. TBI leads to primary brain swelling and secondary complications like oxidative stress and neuroinflammation. We hypothesized that microplastic exposure impairs Paneth cells, disrupting zinc balance in the brain and exacerbating TBI effects. The study involved exposing rats to microplastics for two weeks and then inducing TBI. We assessed neurological impacts, including neuron death and cognitive impairment post-TBI. Results showed that microplastic exposure negatively affects Paneth cell functionality and brain zinc regulation, worsening neuron death in TBI. Interestingly, post-TBI treatment with CTRP9, a protein with potential neuroprotective properties, reduced neuronal death and cognitive decline. This finding underscores the potential of CTRP9 as a therapeutic agent for TBI. In conclusion, our study reveals the harmful effects of microplastics on intestinal and brain health, particularly in the context of TBI, and introduces CTRP9 as a promising candidate for TBI treatment.

Disclosures: M. Park: None. **H. Yang:** None. **S. Woo:** None. **H. Jeong:** None. **B. Choi:** None. **S. Suh:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.21/AA28

Topic: D.04. Brain Injury and Trauma

Support: RS-2025-00520396
RS-2025-25396823

Title: Semaglutide attenuates pilocarpine-induced hippocampal neuronal death by preserving astrocytic glycogen metabolism and reducing zinc neurotoxicity

Authors: *H. YANG[1], M. PARK[2], D.-S. SON[3], H. CHOI[4], S. SUH[5];
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Abstract: Status epilepticus (SE) induces severe neuronal injury driven by zinc-induced metabolic collapse and mitochondrial dysfunction. During SE, excessive synaptic zinc accumulates in postsynaptic neurons, inhibiting glycolytic enzymes and depleting intracellular ATP. Although astrocytes provide critical energetic support via the astrocyte-neuron lactate shuttle (ANLS), this metabolic coupling is compromised during SE. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown neuroprotective potential, but whether it can counteract zinc-induced energy failure by reinforcing astrocytic metabolic support remains unexplored. In the present study, we investigated whether semaglutide protects hippocampal neurons in the pilocarpine-induced status epilepticus model and explored the metabolic mechanisms underlying its neuroprotective effects. We hypothesized that semaglutide enhances astrocytic glycogen metabolism and maintains astrocyte-to-neuron metabolic support, thereby reducing zinc-induced mitochondrial dysfunction and neuronal death. Our findings demonstrate that semaglutide significantly reduces hippocampal neuronal degeneration following status epilepticus. Semaglutide treatment attenuated intracellular zinc accumulation, preserved mitochondrial function, and suppressed apoptotic signaling pathways. Importantly, semaglutide increased astrocytic glycogen levels and enhanced lactate production, suggesting improved astrocyte-mediated metabolic support. Pharmacological inhibition of lactate transport partially abolished the neuroprotective effects of semaglutide, further supporting the role of astrocyte-neuron metabolic coupling in mediating GLP-1 receptor-mediated neuroprotection. These findings demonstrate that semaglutide protects against seizure-induced neuronal injury by reinforcing astrocytic metabolic support to mitigate zinc-induced energy failure. This study identifies semaglutide as a potential therapeutic strategy for status epilepticus.

Disclosures: H. Yang: None. **M. Park:** None. **D. Son:** None. **H. Choi:** None. **S. Suh:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.22/AA29

Topic: D.04. Brain Injury and Trauma

Support: Hartwell Foundation A252590
Hydrocephalus Association A251800
UC Davis Department of Neurological Surgery
BrightFocus Foundation A2023017S
Shriners Hospital for Children 87400-NCA-25

Title: A Large-Animal Model for Translational Research and Therapy Development in Hemorrhagic Cerebral Palsy

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Abstract: Intraventricular hemorrhage (IVH) affects up to 40% of preterm infants and accounts for approximately 10% of all cerebral palsy cases, including a disproportionate share of the most severe and clinically complex patients. Approximately one-third of severe IVH cases progress to posthemorrhagic hydrocephalus (PHH), a life-threatening accumulation of cerebrospinal fluid (CSF) that exacerbates brain injury and contributes to lifelong motor and cognitive disabilities. Current treatment relies on surgical CSF diversion, which is associated with high revision rates and substantial long-term neurosurgical burden. Therefore, a durable, disease-modifying therapy is urgently needed. Translation of promising therapies from preclinical studies to patients has been hindered by the limitations of rodent models, which differ substantially from humans in brain structure, size, and CSF dynamics. Large-animal models, such as piglets, more closely recapitulate human neuroanatomy and ventricular physiology and may provide a critical platform for evaluating therapeutic efficacy, dosing, and safety. To address this need, we are developing and validating a clinically relevant piglet model of PHH in which one-week-old animals receive intracerebroventricular injection of autologous blood. Implantation of a ventricular catheter enables longitudinal CSF drainage and therapeutic delivery, closely modeling current clinical management of PHH and providing a platform for translational studies. A parallel challenge in the field is the rapid and reproducible assessment of ventricular enlargement. Current MRI-based approaches are labor-intensive, time-consuming, and subject to inter-rater variability. To overcome these limitations, we have developed a machine learning-based pipeline for automated ventricular segmentation and volumetric analysis. This approach provides rapid, accurate, and reproducible quantification of ventricular volume that closely matches expert manual segmentation. Ongoing efforts are focused on expanding and generalizing the pipeline across imaging platforms and acquisition protocols to provide the research community with a standardized tool for ventricular assessment. Together, the development of a clinically relevant piglet model of PHH and an automated MRI analysis pipeline establishes a robust translational platform for evaluating novel therapies for IVH and PHH and accelerating their progression toward clinical application in pediatric patients.

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Poster

PSTR312: Brain Injury: Human Studies

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Program #/Poster #: PSTR312.23/AA30

Topic: D.04. Brain Injury and Trauma

Support: MTBI2 MTBI-70-13490
USU- PAT-74-3439.

Title: Repetitive traumatic brain injuries result in severe axonal injury in the human cerebellum

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Abstract: The cerebellum, in addition to its role in coordination and motor activities, has emerged as a key brain structure regulating important neural functions including sleep, cognition, and emotion. It is therefore crucial to understand the effects of traumatic brain injury (TBI) on cerebellar pathology. Blast injury specifically impacts many of those involved in current global conflicts. To evaluate TBI effect on human cerebellum we studied brains of military personnel exposed to multiple blast injuries, or those of control subjects not known to be exposed to blast. We also evaluated brains of military service members using boats for special operations, SWCC (Special Warfare Combatant-craft Crewmen). SWCC operate small, specialized military boats at high velocities and are exposed to repetitive impacts during operation, which regularly produce high g-force measurements, causing “whiplash”-like head movements. None of the individuals involved here were known to have deficits in coordination or motor activity. We specifically evaluated the cerebellar cortex for the structure and distribution of axons using antibodies directed against neurofilament H. The control cerebelli showed many axons extending horizontally throughout the cerebellar cortex and surrounding Purkinje cells, as well as throughout the cerebellar white matter. The labeled axons in control brains populated the full thickness of the molecular layer. In the cerebelli of injured warriors, the pattern of labeled axons reduced substantially, only reaching about one quarter or one third through the molecular layer. In the SWCC brains, the labeled axons were slightly reduced in extent than the blast injured. We also observed that many axons in the blast injured cerebelli showed abnormal appearing swellings not observed in the control brains, where the axons were smooth, without terminal enlargements. The cerebelli of the SWCC also showed abnormal swelling, which were more extensive as the blast injured subjects. The injured axons were also more disorganized, where the control axons showed a smooth parallel organization through the molecular layer. This work emphasizes that pathology of the cerebellum can be extensive, without impact on coordinate or balance, but having strong effects on higher level functions.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR312.24/AA31

Topic: D.04. Brain Injury and Trauma

Support: Brain Injury and Disease Subaward 67470-314223

Title: Perivascular Connexin 43 and Fibronectin expression is a Novel Signature of Interface Astroglial Scarring in a Gyrencephalic Model of Multi-Modal Traumatic Brain Injury

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Abstract: Postmortem findings from U.S. Warfighters with extensive exposure histories to blast and impact reveal the presence of widespread brain scarring. These scarring patterns, demarcated by the presence of reactive astrocytes, occur in unique anatomical patterns linked to blast wave exposure. This phenotype, now known as Interface Astroglial Scarring (IAS), occurs in Layer 1 of the cerebral cortex, the gray/white matter interface, the sulcus of gyri, periventricular zones, and around blood vessels. Our lab developed and characterized a gyrencephalic model of IAS in the ferret by using a combined injury method of repeated blast and CHIMERA exposure. Our model recapitulates the hallmark features of IAS, most notably increases in Glial Fibrillary Acidic Protein (GFAP)+ astrocyte proliferation at sites of interface and a marked increase in Aquaporin 4 (AQP4) around blood vessels. Connexin 43 (CX43) and Fibronectin (FIB) are also biomarkers for astroglial scarring, but have not been assessed in a gyrencephalic model of repeated blast and impact TBI. To this end, we investigated the expression profile of CX43 and FIB in conjunction with the canonical IAS biomarkers GFAP and AQP4 through double and triple-labeling immunohistochemistry and fluorescent microscopy of sham (N=3) and injured (N=6) ferret neocortex. We found a substantial increase of CX43 and Fibronectin labeling associated with AQP4+ blood vessels and GFAP + Astrogliosis at 4 weeks (n=3, 455% increase vs. sham, $p = 0.034$) and 6 months (n=3, 435% increase vs. sham, $p = 0.008$) post-injury, reinforcing previous reports of blood vessels being key sites of primary injury.

Disclosures: B. Smith: None. **D. Perl:** None. **S.L. Juliano:** None.

Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.25/AA32

Topic: D.04. Brain Injury and Trauma

Support: NSF ACCESS 2138259
NSF ACCESS 2138286
NSF ACCESS 2138307
NSF ACCESS 2137603
NSF ACCESS 2138296

Title: A Multi-task Learning Graph Attention Network for Noninvasive Detection and Characterization of Cortical Spread Depression

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Abstract: Cortical spreading depolarizations (CSDs) are slowly propagating waves of neural suppression and a potentially treatable mechanism of secondary brain damage following traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and stroke. Increasing evidence shows that detection and characterization (speed and origin) of these devastating waves can predict worsening brain injury, inform clinical interventions, and improve outcomes. Propagation speed serves as a biomarker for tissue susceptibility and evolving cortical dysfunction, while the cortical origin localizes focal drivers of recurrent CSD events, together enabling spatially and physiologically informed monitoring and interventions. The gold standard for monitoring CSD is through invasive electrocorticography (ECoG) strip electrodes, with limited spatial coverage of the brain. Noninvasive scalp EEG provides global coverage of the brain and enables continuous monitoring of CSD in the Intensive Care Unit (ICU). However, scalp EEG data is noisy and has low spatial resolution, making detection and quantitative estimation of CSD challenging. We present CSD-STGAT, an end-to-end spatio-temporal graph attention network (STGAT) for noninvasive estimation of CSD propagation speed and cortical origin from scalp EEG using a multi-task learning approach. The model employs a shared STGAT backbone, stacked gated temporal convolutions, and graph attention layers over EEG graphs, followed by task-specific attention layers and regression heads. The contribution here is the multi-task learning: both tasks share a joint forward pass through a shared backbone, with separate losses via learnable uncertainty weighting. This forces the shared backbone to learn representations useful for both spatial origin and wavefront speed simultaneously. This is a powerful regularizer grounded in the underlying physics, since CSD speed and origin are coupled through the same propagating wave. We evaluate our technique on 6,000 simulated CSD episodes across three head models using a clinical 20-electrode ICU montage. The joint model achieves a cortical origin localization error of 3.85 mm and a speed normalized error of 1.76%, representing 3-fold and 7-fold reductions in error compared to the state of the art. These simulation results demonstrate that a multi-task learning of a joint graph attention network with task-specific attention pooling provides a scalable, parameter-efficient, and physically grounded framework for noninvasive CSD characterization. This work lays the algorithmic framework for future clinical validation and translation of automated, quantitative CSD monitoring using scalp EEG.

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Poster

PSTR312: Brain Injury: Human Studies

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR312.26/BB1

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant 1R01NS094444
NIH Grant 1R42NS119119
NIH Grant UL1TR001412

Title: Brainstem based microstructural and network level changes in adolescents after sport-related concussion

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Abstract: Sport-related concussion (SRC) is a major public health concern. Standard structural neuroimaging typically reveals no brain abnormalities after SRC. Advanced neuroimaging methods, such as diffusion magnetic resonance imaging (dMRI), allow for the investigation of SRC-associated structural brain changes. Studies using dMRI data have provided insights into microstructural and network-level brain changes; however, the brainstem has been excluded from many of these analyses. We hypothesized that there would be structural brainstem-level differences between adolescent athletes with SRC and matched controls. Multi-shell (b=0, 1000, and 2000 s/mm2 with 8, 21, and 25 directions, respectively) spin-echo echo planar dMRI images were collected on a Canon Vantage Titan 3T scanner. Whole-brain dMRI scans were collected from 13–18-year-old adolescent athletes (n= 35) within 10 days of SRC (V1) and after clinical recovery ~4-6 weeks after injury (V2). Controls (n= 34) had the same data collected at baseline and 4-6 weeks later. Scans were preprocessed, a custom brain atlas was applied, and structural network and diffusion measures were calculated using the Brain Connectivity Toolbox and DSI Studio, respectively. Network measures included strength, clustering coefficient, betweenness centrality, local efficiency, and eigenvector centrality. Diffusion measures consisted of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), quantitative anisotropy (QA), isotropy (ISO), and restricted diffusion imaging (RDI). Statistical analysis was performed using Wilcoxon rank sum tests. For the diffusion measures at V1, significant group differences were seen in the medulla and pons regions of the brainstem for the QA, FA, and MD measures. At V2, differences persisted in the medulla for the FA and MD measures. For the network measures at V1, strength in the left pons differed between groups, with no other brainstem regions having significant differences. At V2, strength was still significantly different in the left pons and also for the right pons. These findings show that SRC is associated with regionally specific brainstem changes, particularly in the pons and medulla, and suggest that the brainstem is a site of microstructural and network-level vulnerability in SRC.

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Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.01/BB2

Topic: E.01. Somatosensation – Pain and Itch

Title: Cortical Signatures of Chronic Pain after Rotator Cuff Injury in Mice

Authors: *J. WEINRICH;
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Abstract: Background and Aims: Rotator cuff injury (RCI) is a leading cause of chronic musculoskeletal pain, yet current therapies remain limited. Surgical repair provides modest benefit, and pharmacologic options such as NSAIDs and opioids rarely offer durable relief. Because pain is ultimately encoded in the brain, we hypothesized that persistent pain after RCI reflects altered cortical processing. We focused on the anterior cingulate cortex (ACC), a region critical for the affective dimension of pain, and sought to link RCI-induced behavioral deficits with ACC activity.
Methods: Adult male mice (N = 5) underwent supraspinatus and infraspinatus tendon transection with denervation (TT+DN) to model massive RCI. Pain-related behaviors and gait were recorded at baseline and two weeks post-injury using the BlackBox One system, which integrates transmitted light imaging and frustrated total internal reflectance to capture paw pose and weightbearing. Automated gait metrics were extracted with our AI-enabled Paw Analysis Workflow. Simultaneously, ACC calcium activity was monitored with an Inscopixminiscope. GCaMP6f was expressed under the CamK2a promoter, and a GRIN lens enabled chronic imaging. Behavioral and neural data streams were synchronized for analysis.
Results: RCI produced robust behavioral and neural alterations. Injured mice demonstrated a significant reduction in forelimb weightbearing (baseline ratio: 0.94 ± 0.10; RCI: 0.63 ± 0.08; $p \leq 0.04$), consistent with impaired function and pain-related guarding. ACC imaging revealed fewer active neurons after injury (baseline: 55 ± 15; RCI: 42 ± 13; $p \leq 0.04$), although average firing rates of identified neurons remained unchanged (baseline: 4.0 ± 0.2 events/min; RCI: 3.8 ± 0.3 events/min; $p = 0.57$). These findings suggest reduced ensemble recruitment in the ACC without changes in mean neuronal activity.
Conclusions: Our integrated platform demonstrates sensitive detection of behavioral and cortical correlates of pain after RCI. Traditional approaches for assessing forelimb pain are laborious and limited, whereas deep behavioral phenotyping provides rapid, unbiased quantification of functional impairment. Linking these measures to ACC dynamics offers mechanistic insight into pain chronification. Ongoing work will extend analyses to later timepoints, female mice, and pharmacologic interventions to determine whether analgesics restore both behavior and ACC function. These studies establish a framework for developing brain-based therapeutic strategies for RCI pain and other orthopedic injuries.

Disclosures: J. Weinrich: None.

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.02/BB3

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Neurosurgery
University of Virginia School of Medicine

Title: Source-level cortical dynamics during laser-evoked temporal summation of pain and conditioned pain modulation in healthy adults

Authors: *D. WANG[1], D. JOHNSTON[3], X. ZHANG[5], W. CARTER[2], G. HWANG[6], G. JUNG[6], M. SHI[6], C.-C. LIU[4];
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Abstract: Temporal summation of pain (TSP) and conditioned pain modulation (CPM) reflect facilitatory and inhibitory pain processes, yet their source-level cortical activity and connectivity remain incompletely understood. We examined current source density (CSD) and functional connectivity during laser-evoked TSP and ice-water CPM in healthy adults. TSP was evoked using painful laser-stimulus triplets, and CPM was assessed using laser test stimuli before and after an ice-water conditioning stimulus. Laser-evoked potentials were analyzed with standardized low-resolution electromagnetic tomography (sLORETA). CSD and trial-level lagged linear connectivity (LLC) were extracted from eight pain-relevant regions of interest: anterior insula, posterior insula, primary somatosensory cortex (SI), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, orbitofrontal cortex (OFC), supplementary motor area (SMA), and amygdala. LLC was assessed across delta, theta, alpha, beta1, beta2, beta3, and broadband omega frequencies. Linear mixed-effects models tested effects of stimulus during TSP, S1-S3, and condition during CPM, pre- versus post-CPM, accounting for repeated measures within participants. For TSP, participants included 22 healthy adults, 50% female, age 22.6±8.9 years. S3 elicited lower CSD than S1 in the amygdala, posterior insula, SI, and SMA, but greater LLC in selected delta-band sensorimotor/salience connections and alpha-band insula-amygdala, amygdala-OFC, and posterior insula-SMA connections. For CPM, participants included 24 healthy adults, 45.8% female, age 23.3±9.2 years. Post-CPM laser responses showed lower CSD across all eight ROIs and broad reductions in source connectivity, including omega-band decreases in 26 of 28 ROI pairs, with additional frequency-specific reductions involving SI-, insula-, amygdala-, OFC-, and SMA-centered networks. These findings suggest that laser-evoked TSP is accompanied by reduced regional source activity but enhanced low-frequency pain-network coupling, whereas ice-water CPM produces widespread reductions in both source activity and source connectivity. Source-level connectivity may provide a complementary marker of facilitatory and inhibitory pain processing in healthy humans.

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Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.03/BB4

Topic: E.01. Somatosensation – Pain and Itch

Title: Individualized Sparse Cortical Codes Embedded Within a Shared Cortical Architecture for Postoperative Pain

Authors: *Y. ZHAO[1], R. PEREZ[4], B. SEIDENBERG[4], E. WANG[4], A. SEEDAT[4], E. JENSEN[4], G. MOMESSO[4], G. SOTO-ARZON[4], B. R. STAVELAND[7], J. JESCHKE[8], F. ZHOU[2], G. KENEFATI[4], L. YU[9], X. LIU[2], M. ROCKHOLT[4], F. DAI[10], J. QIU[4], H. MARTINEZ[4], E. CHOI[4], B. CHEN[4], A. MICHALAK[4], W. K. DOYLE[2], P. C. DUGAN[4], O. DEVINSKY[2], L. DOAN[4], Q. ZHANG[4], Z. S. CHEN[11], E. OERMANN[4], A. FLINKER[3], P. A. ROZMAN[12], R. T. KNIGHT[13], D. FRIEDMAN[5], J. WANG[6];
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Abstract: Postoperative pain recurs spontaneously throughout recovery, remains difficult to measure objectively, and lacks defined neural representations. We recorded longitudinal intracortical activity in 20 patients experiencing spontaneous pain after cranial surgery, enabling systematic within- and cross-individual analyses of cortical representations. Spectral dynamics across anterior cingulate, insular, somatosensory, and orbitofrontal cortices robustly distinguished pain states, revealing a shared cortical architecture underlying postoperative pain. Sparse representation analyses further showed that accurate decoding within individual patients depended on a highly limited subset of region-specific spectral features. Although precise sparse representations did not generalize across individuals, the broader cortical feature space remained conserved. Together, these findings support a model in which postoperative pain emerges from individualized sparse neural representations embedded within a shared cortical architecture.

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Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.04/BB5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R37MH076136
Hitchcock Foundation

Title: Precision Functional Mapping of Distraction from Versus Acceptance of Pain

Authors: *M. SUN[1], S. SHOHAN[2], C. I. BANGO[3], T. D. WAGER[4];
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Abstract: Strategies such as acceptance and distraction are widely used to regulate pain, yet their neural mechanisms have rarely been compared within individuals using precision neuroimaging. Most prior studies rely on group-average analyses that obscure individual variability in pain processing and regulation. We used precision functional mapping to characterize the neural architecture supporting acceptance and distraction from pain across repeated measurements within participants. Nine healthy adults completed a deep-phenotyping fMRI protocol consisting of approximately ten scanning sessions each (over 1,500 total functional runs). Participants performed two pain-regulation paradigms during noxious thermal stimulation. In the acceptance paradigm, participants alternated between experiencing pain naturally and adopting an accepting, nonjudgmental stance toward pain sensations. In the distraction paradigm, participants alternated between painful stimulation during an n-back working memory task and matched control conditions. Whole-brain activation, multilevel modeling, and representational analyses were used to characterize behavioral and neural effects of each strategy. Acceptance produced robust reductions in pain intensity across participants and sessions. Neural effects of acceptance were characterized by widespread modulation of regions implicated in nociceptive processing, affective appraisal, and self-referential cognition, including insular, cingulate, and default-network territories. In contrast, distraction preferentially engaged frontoparietal executive-control systems associated with working memory and attentional allocation. Despite producing behavioral analgesia, distraction showed more limited modulation of pain-related neural representations. Direct comparisons revealed dissociable neural pathways supporting pain regulation through attentional disengagement versus experiential openness. Individualized analyses further demonstrated substantial heterogeneity in the spatial organization of these effects while preserving common network-level motifs across participants. Acceptance and distraction regulate pain through distinct large-scale brain systems. Precision functional mapping reveals that acceptance is associated with broader reorganization of pain-related neural processing, whereas distraction primarily recruits executive-control mechanisms. These findings provide a high-resolution account of two pain-regulation strategies and illustrate the value of intensive within-person neuroimaging for understanding mechanisms of cognitive pain regulation.

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Poster

PSTR313: Cortical Processing of Pain

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Program #/Poster #: PSTR313.05/BB6

Topic: E.01. Somatosensation – Pain and Itch

Support: CODICE WFR:PNRR-MCNT2-2023-12378259; CODICE CUP:B13C24001060006

Title: (f)MRI-guided anodal HD-tDCS of the dorsal anterior cingulate cortex modulates pain-related brain responses in chronic pain

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Abstract: Chronic pain is a disabling condition in which persistent sensory-affective symptoms are often accompanied by emotional distress and functional impairment. Because conventional interventions frequently provide limited long-term benefit, non-invasive neuromodulation represents a repeatable and well-tolerated adjunctive treatment, with no evidence of significant adverse effects. Current guidelines support anodal tDCS of the primary motor cortex for selected chronic pain conditions, with probable and possible efficacy in fibromyalgia and chronic lower-limb neuropathic pain, respectively. The dorsal anterior cingulate cortex (dACC), a key node of the affective sector of the so-called “pain matrix”, is implicated in pain hypersensitivity and neurostimulation response, but whether high-definition transcranial direct current stimulation (HD-tDCS) of dACC modulates pain sensitivity and its underlying neural mechanisms has never been assessed. We thus tested whether a personalized (f)MRI-guided HD-tDCS protocol targeting the dACC modulates clinical pain outcomes and pain-related brain responses in chronic pain. In this ongoing single-blind study, two groups of patients undergo 20-min sessions of either anodal or sham/placebo HD-tDCS in 5 consecutive days. Clinical outcomes include pain intensity/interference, physical and emotional functioning, perceived improvement and treatment-related symptoms. Before and after treatment, 3T (f)MRI includes T1-weighted imaging, resting-state fMRI and task fMRI during observation of pain-related vs. neutral facial expressions or bodily stimulation. Task-related activations provide the target coordinates for HD-tDCS of the dACC, and T1 images allow personalizing the HD-tDCS montage by modeling

current flow according to individual brain anatomy. Preliminary behavioral analyses in 35 patients (anodal: n=19; sham/placebo: n=16) showed a significant reduction in pain interference, pain catastrophizing, helplessness and activity-related impairment from pre- to post-treatment ($p<0.05$), but without a stronger effect of real vs. sham HD-tDCS ($p>0.05$). Instead, fMRI analyses showed a significant group x timepoint interaction in the dACC, with activity in this region decreasing after anodal HD-tDCS and increasing after sham/placebo stimulation. These findings provide preliminary evidence that anodal HD-tDCS of dACC downregulates affective pain-related cortical responses. If paralleled by clinical improvement, this MRI-guided approach may support individualized, low-cost adjunctive neuromodulation strategies for chronic pain.

Disclosures: N. Canessa: None. **G. D'Este:** None. **C. Lenti:** None. **M. Colletti:** None. **F. Civiletti:** None. **R. Bonaventura:** None. **G. Topi:** None. **L. D'Auria:** None. **G. Locatelli:** None. **E. Arrigoni:** None. **G. Giglia\:** None. **M. Oliveri:** None. **A. Pisoni:** None. **G. Mattavelli:** None. **V. Lo Re:** None. **L. Romero Lauro:** None. **S. Natoli:** None.

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.06/BB7

Topic: E.01. Somatosensation – Pain and Itch

Support: Natural Science Foundation of Shanghai (25ZR1402460）

Title: Anterior Cingulate Cortex Encodes Negative Affective Valence and Drives Aversive Behavior

Authors: *H. LIU;
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Abstract: The anterior cingulate cortex (ACC) is a critical hub for pain and affective emotion. However, how ACC excitatory neurons integrate diverse inputs and engage specific downstream pathways to transform nociceptive signals into negative emotional states remains incompletely understood. Here, we combined optogenetics, fiber photometry, and behavioral assays to investigate the causal role of ACC excitatory CaMKIIα neurons in pain and affective states. Optogenetic activation of ACC excitatory neurons was sufficient to induce conditioned place aversion (CPA) and drive aversive behavior. To test the necessity of ACC excitatory neurons in naturalistic aversion, optogenetic inhibition of these neurons significantly reversed formalin-induced CPA and alleviated chronic constriction injury(CCI)-induced anxiety- and depressive-like behaviors, as assessed by the open field test, elevated plus maze, and sucrose preference test. To monitor how these neurons encode nagative stimulates, we performed fiber photometry. ACC excitatory neuron activity increased robustly in response to noxious stimulation (von Frey filament on the inflamed paw), aversive stimulation (licking the inflamed paw, open arm exposure on the elevated plus maze, and facial air puff). In contrast, tastant stimuli with positive

(sucrose) or negative (quinine) valence elicited an immediate decrease in ACC calcium signals. Finally, anterograde and retrograde tracing revealed that the ACC sends dense excitatory projections to the periaqueductal gray (PAG), basolateral amygdala (BLA), zona incerta(ZI), and paramedian raphe nucleus (PMnR). Together, these results demonstrate that ACC excitatory neurons encodenegative affective valence across multiple aversive modalities and are necessary for pain-related emotional behaviors. Our findings position the ACC as a key node in the negative valence processing system.

Disclosures: H. Liu: A. Employment/Salary (full or part-time):; Songjiang Research Institute, Shanghai Jiao Tong University School of Medicine, Shanghai 201600, China..

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.07/BB8

Topic: E.01. Somatosensation – Pain and Itch

Support: NIGMS Grant R01-GM115384
NINDS Grant R01-NS121776
Interdisciplinary Pain Research Program at NYU Grossman School of Medicine

Title: The Insular-Anterior Cingulate Cortex Pathway Regulates Pain Aversion

Authors: E. CHOI[1], Z. YU[3], J. KAHANE[1], J. PLOTKIN[4], E. HU[5], ***Q. ZHANG**[2], J. WANG[6]; [1]Anesthesiol., [2]NYU Sch. of Med., New York, NY; [3]New York Univ., New York City, NY, ; [4]NYU, New York City, NY; [6]Anesthesiol., [5]NYU Grossman Sch. of Med., New York, NY

Abstract: Pain perception and modulation involve distributed neural networks that extend beyond traditional cortico-subcortical pathways to include complex interactions among cortical regions. The affective component of pain is a major contributor to suffering and disability, yet the cortical circuit mechanisms underlying pain aversion remain incompletely understood. The anterior insular cortex (aIC) and anterior cingulate cortex (ACC) are critically involved in pain processing and are strongly interconnected. We hypothesized that the aIC to ACC projection facilitates the encoding of pain aversion by modulating ACC network activity. To test this hypothesis, we combined conditioned place aversion (CPA) behavioral testing with optogenetic manipulation of the aIC to ACC pathway in freely behaving rats. We found that selective activation of aIC projections to the ACC significantly enhanced pain-induced aversive behavior. These findings identify the aIC to ACC pathway as a critical cortical circuit regulating the affective dimension of pain and highlight the importance of cortico-cortical interactions in shaping pain-related negative emotional states.

Disclosures: E. Choi: None. **Z. Yu:** None. **J. Kahane:** None. **J. Plotkin:** None. **E. Hu:** None. **Q. Zhang:** None. **J. Wang:** None.

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.08/BB9

Topic: E.01. Somatosensation – Pain and Itch

Support: National Natural Science Foundation of China (81971049, 81671097)

Title: TGF-β1 in the Anterior Cingulate Cortex Regulates the Somatic Hyperalgesia Induced by Orofacial Inflammation Combined with Chronic Heterotypic Stress

Authors: P. WANG[1], S. WEI[1], Q. YANG[2], L. ZHONG[1], R. J. TRAUB[3], J.-Y. WANG[2], ***D.-Y. CAO**[3];
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Abstract: Our previous studies have established an animal model of orofacial inflammation combined with different modes of stress to induce somatic hyperalgesia, which successfully simulated typical clinical features of comorbidity of temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS). The present study focused on the different stages in the progression of comorbid pain hypersensitivity (CPH) and the role of transforming growth factor-β1 (TGF-β1) in the anterior cingulate cortex (ACC) in the development of CPH. Orofacial inflammation was induced by complete Freund's adjuvant (CFA, 150 μL, 1:1 in saline) injected into bilateral masseter muscles in female Sprague-Dawley rats, with equal amount of normal saline as control. After CFA or saline injection, rats were given 7-day or 12-day heterotypic stress, including forced swim stress (FSS) for 20 min, water avoidance stress (WAS) for 1 h and restraint stress (RS) for 2 h. FSS was given every 3 days and the other two stressors were alternated within each cycle. Mechanical threshold was tested by von Frey filaments and thermal withdraw latency of hindpaw was measured before CFA injection (as baseline) and after stress till restoring to baseline. Tissues of the ACC were collected 1 day after last stressor. mRNA levels of cytokines were examined by quantitative real-time PCR (qPCR) and the protein levels of TGF-β1 and its receptor were examined by Western blot. The positive staining of TGF-β1 was observed by immunofluorescence. The pain behaviors were also tested after injection of recombinant rat TGF-β1 (rrTGF-β1) or TGF-β1 antibody (anti-TGF-β1 Ab) into the ACC in CPH rats. Orofacial inflammation combined with 7-day heterotypic stress (7-day CPH) caused significant somatic hyperalgesia, while orofacial inflammation combined with 12-day heterotypic stress (12-day CPH) induced longer duration of somatic hyperalgesia. The protein expression and positive cell rate of TGF-β1 in the ACC significantly decreased in 12-day CPH rats, whereas significantly increased in 7-day CPH rats. Injection of rrTGF-β1 into the ACC significantly alleviated the somatic hyperalgesia in 12-day CPH rats. Injection of anti-TGF-β1 Ab into the ACC significantly alleviated the somatic hyperalgesia in 7-day CPH rats. In addition, injection of anti-TGF-β1 Ab into the ACC induced obvious somatic pain-like behaviors in naïve female rats. These results indicate that TGF-β1 in the ACC serves a neuroprotective function

against injury under normal physiological conditions. However, it exhibits distinct roles at different stages of the TMD-FMS comorbidity.

Disclosures: P. Wang: None. **S. Wei:** None. **Q. Yang:** None. **L. Zhong:** None. **R.J. Traub:** None. **J. Wang:** None. **D. Cao:** None.

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.09/BB10

Topic: E.01. Somatosensation – Pain and Itch

Title: LSD persistently disrupts affective pain processing

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Abstract: Psychedelics produce long-lasting effects, but their circuit mechanisms remain unclear. Here we show that, in rats, a single dose of lysergic acid diethylamide (LSD) persistently reduces pain affect. This effect is recapitulated by local administration in the anterior cingulate cortex (ACC), but not primary somatosensory cortex. Neuropixels recordings reveal that LSD suppresses stimulus-evoked nociceptive responses in the ACC, reducing the encoding of aversive value. Despite increasing intrinsic excitability ex vivo, LSD reduces the maximum stimulus-evoked firing of ACC neurons in vivo, indicating a dissociation between excitability and sensory encoding. Together, these findings show that psychedelics disrupt the cortical transformation of nociceptive input into aversive representations.

Disclosures: J. Plotkin: None. **E. Zhu:** None. **M. Druart:** None. **T. Sippy:** None. **J. Wang:** None.

Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.10/BB11

Topic: E.01. Somatosensation – Pain and Itch

Support: RS-2025-25459221
RS-2025-00562132
5U19AG065169
P30AG066507

Title: Ibogaine reopens NPTX2-gated plasticity to reverse chronic neuropathic pain in mouse somatosensory cortex

Authors: *H. SHIN[1], Y. LAO[2], T. YOO[3], S. CHOI[4], S.-E. ROH[5], P. F. WORLEY[6], S. KIM[7]; [1]Dept. of Sci. in Korean Medicine, Grad. School, Kyung Hee Univ., Seoul, Korea, Republic of; [2]Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins, Baltimore, MD; [4]Deaparment of Physiol., Kyung Hee Univ., Seoul, Korea, Republic of; [5]Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD; [6]Dept Neurosci/Neurol, Johns Hopkins Sch. Med., Baltimore, MD; [7]Dept. of Physiol., Kyung Hee Univ. Col. of Korean Med., Seoul, Korea, Republic of

Abstract: Neuropathic pain is a persistent and disabling condition that reflects maladaptive cortical plasticity. Loss of inhibitory control and disrupted excitation-inhibition balance in primary somatosensory cortex (S1) is a key feature, yet the molecular mechanisms enabling recovery remain unclear. Neuronal Pentraxin 2 (NPTX2), an activity-regulated synaptic organizer, strengthens pyramidal→parvalbumin (PV) interneuron coupling by clustering AMPA receptors at PV synapses, thereby stabilizing cortical networks. We hypothesized that neuropathic pain reflects a breakdown of NPTX2-dependent homeostatic plasticity and that ibogaine, an atypical psychedelic known to reopen critical-period-like plasticity, restores circuit stability through NPTX2 regulation. In a mouse model of neuropathic pain (partial sciatic nerve ligation), a single administration of ibogaine (40 mg/kg, i.p.) produced robust and long-lasting analgesia, persisting for weeks. Disruption of NPTX2 function in S1 abolished ibogaine-induced analgesia, while NPTX2 overexpression induced hypersensitivity in sham control mice and blocked ibogaine's therapeutic effect in injured mice. These findings identify a novel mechanism linking psychedelic-induced cortical plasticity to long-lasting pain relief and highlights NPTX2 as a therapeutic target for chronic neuropathic pain.

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Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.11/BB12

Topic: E.01. Somatosensation – Pain and Itch

Support: Abbott Neuromodulation

Title: Carryover Effects During OFF Phase of Cycled Burst Spinal Cord Stimulation in a Rodent Model of Neuropathic Pain

Authors: C. LUU[1], K. LUDWIG[1], M. ZHANG[3], ***A. J. SUMINSKI**[2];
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Abstract: Neuromodulation approaches such as spinal cord stimulation (SCS) are increasingly used as alternatives to the traditional pharmacologic treatments of chronic pain. Conventional SCS typically delivers continuous electrical stimulation via epidural electrodes targeting dorsal column pathways. In contrast, BurstDR™ SCS applies brief trains of stimulation separated by longer OFF periods and has demonstrated effective pain relief with improved patient experience. The efficacy observed during OFF periods suggest the presence of carryover effect of SCS therapy; however, the underlying mechanisms and optimal duty cycles remain poorly understood.The goal of this work is to determine how modulation of burst SCS duty cycle influences neural responses to noxious stimuli and contribute sustained therapeutic effects during OFF phases. To address this, we developed a combined stimulation and recording paradigm to assess neural signatures associated with various ON/OFF parameters. In urethane-anesthetized Long Evans rats, a custom, two-contact paddle electrode was implanted epidurally at the T13 to L1 spinal level for SCS delivery. Neural activity was simultaneously recorded using a 32-channel microwire array (TDT, Alachua, FL) in the somatosensory cortex (-1 mm AP, -3 mm ML, 0.8-1.2 mm DV). Preliminary data demonstrated the feasibility of high throughput framework for quantifying activation thresholds and cortical response patterns associated with medial and lateral pain pathways across stimulation conditions.These results will help to support the presence of the carryover effects during OFF phases of burst SCS and provide a platform for systematically optimizing duty cycle parameters. This approach may help elucidate mechanisms underlying therapeutic efficacy and inform next-generation neuromodulation strategies for chronic pain.

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Poster

PSTR313: Cortical Processing of Pain

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR313.12/BB13

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5R01NS136997-02

Title: Modulation of Somatostatin-Expressing Interneurons in S1 Regulates Sensory Thresholds and Drives Discriminative Neural Correlates of Painful and Non-Painful Stimuli

Authors: *C. PETERSEN[1], K.-S. JEONG[2], J. MEIER[1], A. S. ABDELFATTAH[1], C. Y. SAAB[2], D. A. BORTON[1];
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Abstract: The primary somatosensory cortex (S1) plays a significant role in pain perception, but while S1 gamma band activity is a proven neural correlate of pain, similar activity signatures in S1 appear during non-painful touch. This convergence of activity complicates the disambiguation of the specific neural mechanisms of pain from non-painful touch. We have previously developed a self-report behavioral assay by which TRPV1-CHR2 expressing mice are trained to differentially report laser-evoked noxious and innocuous tactile stimuli via a lick behavior. We demonstrated that trial-averaged gamma power in S1 increases following both stimulus modalities. However, and critically, on individual trials, the evoked transient gamma band spectral events distinguished noxious from innocuous stimuli. Here, we aim to understand the source of these gamma oscillations. Previous work has implicated Parvalbumin-expressing (PV) and Somatostatin-expressing (SOM) inhibitory interneurons in the transmission of nociceptive information, but the direct representation of pain and tactile behaviors by PV and SOM cells has yet to be demonstrated. We address this knowledge gap using *in vivo* genetically encoded voltage indicators (GEVIs) to show temporal correlation between spiking and sub-threshold responses of SOM cells in layers 2/3 of the mouse S1 in response to time locked tactile and noxious stimuli. Further, we show that peripherally induced activation of SOM neurons independently increased sensory thresholds. These findings provide insight into the microcircuitry driving pain behavior-associated brain rhythms, broadening our understanding of the disease trajectory of chronic pain and uncovering mechanisms of proposed therapeutic targets.

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Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.01/BB14

Topic: E.01. Somatosensation – Pain and Itch

Title: The Mechanisms of chronic itch induced cognitive impairment

Authors: *D. D. LI[1,2,3], O. CHEN[4,6,2], Y. TANG[5,7,2];
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Univ., Beijing, China; [2]Chinese Inst. for Brain Res., Beijing, China; [3]Hebei Med. Univ., Shijiazhuang, China; [5]Dept. of Neurol. & Innovation Ctr. for Neurolog. Disorders, [4]Xuanwu Hosp. Capital Med. Univ., Beijing, China; [6]Duke Univ. Sch. of Med., Durham, NC; [7]Beijing Key Lab. of Digital Med. for Cognitive Disorders, Beijing, China

Abstract: The Mechanisms of chronic itch induced cognitive impairment Authors Dan Li[1,4], Run Di[1,4], Jun-Jie Hu[1,4], Yu-sen Deng[1,4], Ouyang Chen[1,2,4], Yi Tang[1,3,4]; [1]Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, Capital Medical University, National Center for Neurological Disorders, Beijing, China, [2]Department of Cell Biology, Duke University School of Medicine, Durham, North Carolina, United States, [3]Beijing Key Laboratory of Digital Medicine for Cognitive Disorders, Beijing, China, and [4]Chinese Institute for Brain Research, Beijing, China. **Disclosures** Dan Li: None. Run Di: None. Jun-Jie Hu: None. Yu-sen Deng: None. Ouyang Chen: None. Yi Tang: None. **Abstract** Chronic itch affects approximately 22% of people in their lifetime, which is associated with a significantly diminished quality of life, leading to disrupted sleep patterns and mood disturbances. Of note, previous clinical and animal experimental studies have shown a close correlation between chronic itch and accelerated cognitive decline. However, the mechanisms underlying chronic itch-associated cognitive impairment remain unclear. Using the oxazolone induced the mouse (C57BL/6, Aged 2-month to 4-month) model of allergic contact dermatitis (ACD), we established a chronic pruritus condition persisting for up to two months. Behavioral assessments including the Barnes maze, novel object recognition tests, and Y-maze tests revealed significant impairments in spatial memory after 60 days in ACD mice. Furthermore, morphological and electrophysiological analyses demonstrated neuronal hyperexcitation and impaired synaptic plasticity in ACD mice. To investigate the mechanism of cognitive impairment in ACD mice, we employed single-cell RNA sequencing, immunofluorescence staining, and ELISA. The colocalization analysis of C1q and synaptic proteins including Glutamate Transporter 1, Vesicular GABA Transporter, Homer scaffold protein 1 and Gephyrin, suggesting that microglial activation-dependent C1q release mediated the excessive synaptic pruning, contributing to the observed cognitive decline. Overall, these findings may provide a theoretical foundation and potential therapeutic targets for understanding chronic pruritus-related cognitive impairments.

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Poster

PSTR314: Inflammatory Pain and Itch

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Program #/Poster #: PSTR314.02/BB15

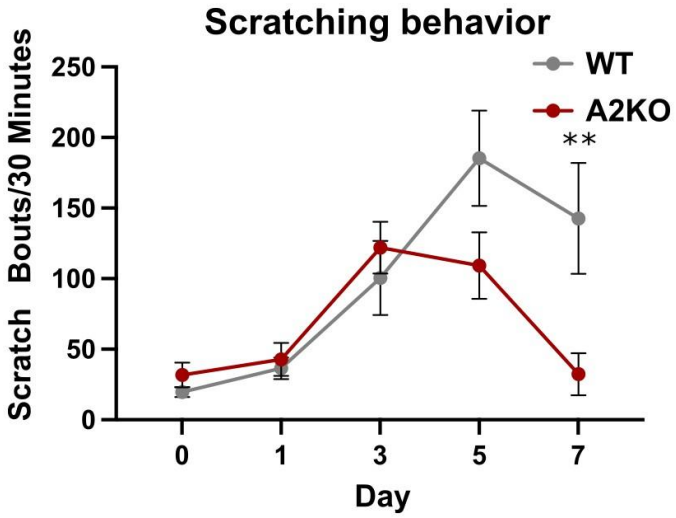
Topic: E.01. Somatosensation – Pain and Itch

Support: Howard Hughes Medical Institute
NIH T32NS070201
Woodrow Wilson Undergraduate Research Fellowship

Title: The role of the neutrophil receptor Mrgpra2 in neuroimmune regulation of atopic dermatitis-associated itch

Authors: *H. LE CHANG, T. FOLLANSBEE, X. DONG;
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Abstract: Atopic dermatitis (AD) is a chronic inflammatory skin disease often accompanied by persistent itch. Recent studies have identified neutrophils as key contributors to neuroinflammation and sensitization of pruriceptors in AD. In AD models, neutrophils promote pruriceptor sensitization through the release of inflammatory mediators, such as Cxcl10. Mas-related G protein-coupled receptor A2 (Mrgpra2) is a neutrophil-specific receptor that regulates neutrophil responses during bacterial skin infection, but its role in AD-associated itch remains unexplored. We investigated whether Mrgpra2 contributed to the development of itch in the MC903 mouse model of AD. Wildtype (WT) and Mrgpra2 knockout (A2KO) mice received daily topical MC903 treatment for seven days. Scratching behavior, epidermal thickness, transepidermal water loss (TEWL), neutrophil infiltration, and inflammatory gene expression was assessed throughout disease progression. A2KO mice exhibited significantly reduced scratching behavior compared to WT controls following MC903 treatment. Epidermal thickness and TEWL were also reduced in A2KO mice. Together, these findings indicate a role of Mrgpra2 in the disease severity of AD. To evaluate whether the improvements we observed in A2KO mice were due to inhibited neutrophil recruitment, immunohistochemistry and flow cytometry were performed. Surprisingly, we observed no significant differences in neutrophil accumulation in the skin between genotypes. However, expression of thymic stromal lymphopoietin (TSLP), a key mediator of AD-associated inflammation and itch sensitization, was reduced in A2KO mice during early disease progression. These findings identify Mrgpra2 as a regulator of chronic itch and skin pathology in AD. Since Mrpgpra2 knockout reduced disease severity despite unchanged neutrophil recruitment, we hypothesize that Mrgpra2 contributes to AD-associated itch through modulation of neutrophil cytokine release, which may reduce sensitization of pruriceptive primary afferent neurons.



Disclosures: H. Le Chang: None. **T. Follansbee:** None. **X. Dong:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

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Program #/Poster #: PSTR314.03/BB16

Topic: E.01. Somatosensation – Pain and Itch

Support: Natural Science Foundation of China (No.82471235 to L.Q.)
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Hunan Province Acute and Chronic Pain Clinical Research Institute (No. 2023SK4014 to W.L)

Title: The neuropeptide neuromedin U promotes arthritis pain and inflammation via mast cell specific receptor MRGPRX2

Authors: L. YANG[1], W. LIU[1], ***L. QU**[2,1];
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Abstract: Chronic joint pain is a dominant symptom of rheumatoid arthritis (RA), yet its underlying mechanisms remain poorly understood. The intricate interplay between sensory neurons and immune cells has been implicated in the pathogenesis of chronic pain and inflammation, with neuropeptides emerging as key drivers in this process. The neuropeptide neuromedin U (NMU) contributes to mast cell (MC)-mediated inflammation independently of its canonical receptor NMUR1. However, whether and how NMU promotes RA pain and joint inflammation is not well defined. Here, we show that NMU levels were elevated in the inflamed joints and dorsal root ganglia but not in the serum of mice with collagen II-induced arthritis (CIA). NMU was predominantly expressed in a subset of small-diameter joint-innervating sensory neurons. Selective deletion of *Nmu* in primary sensory neurons significantly attenuated arthritis pain and joint inflammation in a mouse model of antigen-induced arthritis (AIA). Chemogenetic silencing or ablation of NMU^{+} sensory neurons produced similar effects in AIA model mice. Mechanistically, we identified NMU as a novel endogenous agonist of Mrgprb2, the mouse mast cell specific receptor. NMU drove both joint pain and inflammation through activation of synovial MCs. Translational studies revealed an upregulation of the human ortholog MRGPRX2 and NMU expression in the inflamed joints of RA patients. NMU induced degranulation of human MCs via MRGPRX2 but not its canonical receptor NMUR1, which triggered both joint hypernociception and inflammation. Together, our data expand the understanding of the immunosensory capabilities of sensory neurons and highlight the NMU-Mrgprb2 axis as a promising therapeutic target for RA pain.

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Poster

PSTR314: Inflammatory Pain and Itch

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Program #/Poster #: PSTR314.04/BB17

Topic: E.01. Somatosensation – Pain and Itch

Support: Prof. K. H. René Koczorek Foundation

Title: Tumor-Macrophage-Nerve Crosstalk Drive Neuroinflammation and Neuropathic Pain in Prostate Cancer Perineural Invasion via CREB-ERK1/2 Signaling

Authors: S. MOUSA[1], M. SHAQURA[2], S. TRESKATSCH[3], ***M. SCHAEFER**[4];
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Abstract: Perineural invasion, a hallmark of cancers including prostate and pancreatic cancer, is strongly associated with severe, treatment-refractory pain. To investigate the mechanisms underlying perineural invasion-associated pain, we established a syngeneic rat model of prostate cancer perineural invasion. This model was used to characterize neuroinflammatory processes arising from direct tumor-nerve interactions and to provide a platform for evaluating targeted therapeutic strategies. GFP-expressing AT-1 prostate cancer cells were microinjected directly into the perineurium of the sciatic nerve in syngeneic Copenhagen rats. Over 21 days, tumor progression, macrophage infiltration, and the expression of proinflammatory, protumorigenic, and neuronal injury-associated mediators were assessed. Nociceptive responses to mechanical, heat, and cold stimuli were evaluated over 21 days. MEK/ERK signaling was pharmacologically inhibited by intrathecal administration of the MEK inhibitor PD98059. Perineural injection of AT-1 cells resulted in progressive tumor growth accompanied by increased macrophage infiltration and polarization, with a predominance of M1-like macrophages and elevated expression of the proinflammatory cytokines IL-1β and TNF-α. This response was associated with increased levels of RANTES, IL-1ra, TIMP-1, VEGF, and the proliferation marker Ki-67, together with upregulation of the neuronal injury and neurotrophic markers ATF3, NGF, and GDNF in the sciatic nerve. Mechanical and cold allodynia, as well as heat hyperalgesia, progressively intensified over the 21-day observation period. These behavioral changes were accompanied by increased c-Fos and GFAP expression and enhanced phosphorylation of CREB and ERK1/2 along nociceptive pathways. Intrathecal administration of PD98059 significantly reversed perineural tumor-induced mechanical allodynia. Collectively, these findings demonstrate that this model reproduces key clinical and biological features of prostate cancer perineural invasion and provides novel insights into neuroinflammatory tumor-macrophage-nerve interactions that promote neuronal and glial activation and nociceptive sensitivity. Although the model enables detailed mechanistic investigation of tumor-induced neuronal and

glial responses, it may not fully reproduce the multifocal and treatment-refractory pain associated with advanced disease and complex nerve plexus invasion.

Disclosures: S. Mousa: None. **M. Shaqura:** None. **S. Treskatsch:** None. **M. Schaefer:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.05/BB18

Topic: E.01. Somatosensation – Pain and Itch

Support: NS121946
NS136108

Title: Sex-Dependent Fibromyalgia-Like Pain and Neuroimmune Responses in the Reserpine-Induced Mouse Model

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Abstract: Fibromyalgia (FM) is a chronic pain disorder affecting approximately 5% of the world population, with a higher prevalence in women. Beyond musculoskeletal pain, patients commonly experience comorbidities such as anxiety, fatigue, and depression. Despite its high burden, FM remains poorly understood and treatment options are limited, underscoring the need for preclinical models that capture key clinical features and enable mechanistic discovery. In this study, we used the reserpine-induced mouse model to characterize fibromyalgia-like phenotypes. Our results show that reserpine administration induces robust pain hypersensitivity with sex-specific differences in recovery trajectory: female mice exhibited persistent hypersensitivity for months, whereas male mice fully recovered over 2-3 weeks. Additional behavioral assays, including the open field test and tail suspension test, revealed fatigue-like and depression-like phenotypes, supporting the translational relevance of this model. Given emerging evidence suggesting innate immune dysfunction in FM, we examined the time course of neuroimmune responses in dorsal root ganglion (DRG) tissues. Our results reveal sex-dependent peripheral dysregulation of inflammatory immune responses. Unlike male reserpine-treated mice, female reserpine-treated mice exhibited elevated macrophage infiltration and satellite glial cell activation in the DRGs. Finally, to identify potential molecular drivers of this sex-dependent behavioral and neuroimmune profile, we performed RNA sequencing on DRG tissues. Together, these findings support the reserpine-induced mouse model as a relevant approach for studying FM and highlight early, sex-dependent peripheral neuroimmune mechanisms that may contribute to the development of FM-like pain.

Disclosures: Y. Sahlloul: None. **A. Prudente:** None. **E.S. Brum:** None. **S. Oliveira:** None. **T. Berta:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.06/BB19

Topic: E.01. Somatosensation – Pain and Itch

Title: Peripheral Sensitization, Neuroinflammation, and Central Pain Dysregulation in Rodent Models of Endometriosis: A Comparative Induction Study

Authors: *S.-Y. NA, H. LEE, Y. KIM, K. RADHAKRISHNAN, J. LEE, K. PARK, P. J. SWEENEY, L. PARK;
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Abstract: Endometriosis is an estrogen-dependent inflammatory disorder characterized by ectopic lesions that promote peripheral sensitization through aberrant innervation, neuroinflammatory signaling, and nociceptor activation. Lesion-derived mediators, including prostaglandins, nerve growth factor (NGF), and cytokines, sensitize primary afferent C- and Aδ-fibers, contributing to chronic pelvic pain and allodynia. Sustained peripheral input may further drive central sensitization and widespread pain hypersensitivity. To evaluate the neurobiological relevance of commonly used preclinical models, we compared syngeneic endometriosis induction approaches in mice and rats using longitudinal sensory behavioral assessments and terminal histopathologic, immunohistochemical, and molecular analyses of pain-related neural and inflammatory markers. Marked differences were observed between species and induction conditions. Mouse syngeneic inoculation produced robust endometrioma-like lesion burden and is well suited for screening lesion-targeted therapies; however, pain-related behavioral changes were relatively modest, suggesting limited engagement of peripheral sensitization pathways. In contrast, the rat model, particularly with hormonal priming to mimic estrogen-driven neuroinflammatory conditions, generated smaller lesions but significantly greater mechanical hypersensitivity and non-evoked pain behavior. These findings are consistent with enhanced nociceptor sensitization, increased afferent input, and activation of central pain-processing mechanisms. Immunohistochemical and molecular analyses further differentiated the models, revealing distinct profiles of innervation and neuroinflammatory markers that paralleled behavioral outcomes. Collectively, these results support a fit-for-purpose framework for preclinical endometriosis research. Mouse syngeneic inoculation is most appropriate for lesion-focused efficacy studies, whereas hormonally primed rat inoculation more closely recapitulates the neurobiological mechanisms underlying endometriosis-associated pain. Together, these complementary models provide translationally relevant platforms for investigating nociceptive mechanisms and evaluating novel analgesic and neuromodulatory therapies.

Disclosures: S. Na: None. **H. Lee:** None. **Y. Kim:** None. **K. Radhakrishnan:** None. **J. Lee:** None. **K. Park:** None. **P.J. Sweeney:** None. **L. Park:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.07/BB20

Topic: E.01. Somatosensation – Pain and Itch

Support: University of Pittsburgh Department of Anesthesiology and Perioperative Medicine
FAER Mentored Research Training Grant
NIH Grant 1R35GM150680

Title: Loss of neuronal MD-1 activates p38 MAPK in the DRG and increases Ly6G mRNA in skin in response to plantar incision

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Abstract: Sensory neurons play a critical role in the cutaneous immune response during inflammation. Recent studies indicate that nonpeptidergic neurons provide anti-inflammatory signaling in this response. Analysis of sensory ganglia in mice that overexpress neurturin (Nrtn), a growth factor that supports the development and survival of nonpeptidergic neurons, revealed increased expression of immune-related genes, suggesting that these neurons have a role in maintaining immune homeostasis and regulating responses to immune challenge.
To further investigate this neuroimmune role, we analyzed dorsal root ganglia (DRG) from mice overexpressing Nrtn and found significant upregulation of lymphoid antigen, *Ly86*, which encodes myeloid differentiation protein-1 (MD-1), a component of the innate immune system. To examine the role of neuronal MD-1 in immune signaling, we used a mouse plantar incision model and assessed the effects of conditional knockout of MD-1 in MrgprD+ nonpeptidergic neurons on the immune responses and incision-induced hypersensitivity.
MD-1 knockout mice exhibited increased expression of *Ly6G*, a marker of neutrophils, in the cutaneous tissue. In addition, at 7 days post incision, these mice showed elevated levels of *TNFA* mRNA and phosphorylated p38 MAPK, a transcription factor regulator, activated in response to inflammatory cytokine signaling. Behavioral analysis also revealed greater mechanical sensitivity at the incision site at 7d and 11d after injury, consistent with increased neutrophil infiltration and enhanced p38 signaling.
Collectively, these findings suggest that loss of MD-1 in nonpeptidergic cutaneous afferents amplifies inflammatory and behavioral responses to skin injury. Ongoing studies aim to define

the mechanisms through which neuronal MD-1 regulates cutaneous immune responses and hypersensitivity.

Disclosures: M. Menon: None. **J. Jones:** None. **K.M. Albers:** None. **M. Ritter:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.08/BB21

Topic: E.01. Somatosensation – Pain and Itch

Support: SIP-IPN 20260588

Title: Preclinical antinociceptive synergistic interaction between a sigma one antagonist and an opioid agonists

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Abstract: This study investigated the pharmacological interactions between haloperidol, a sigma-1 antagonist, and buprenorphine or tramadol, an opioid agonist, in a rat model of inflammatory nociception. Dose-response curves were generated for haloperidol, buprenorphine, and tramadol administered individually in rats subjected to the 1% formalin test. All compounds produced dose-dependent antinociceptive effects. Drug interactions were evaluated using isobolographic analysis. The median effective doses (ED50) of each drug were combined at a fixed 1:1 ratio to generate combination dose-response curves for haloperidol + buprenorphine and haloperidol + tramadol. ED50 values revealed significant differences in the antinociceptive potency of the drugs. Buprenorphine (ED50 = 9.9 ± 1.1 µg/kg) was significantly more potent than haloperidol (ED50 = 45.3 ± 2.8 µg/kg) and tramadol (ED50 = 9930 ± 602 µg/kg), notably, at the maximum analyzed doses, buprenorphine-and haloperidol-induced sedation in rats, an effect that was not observed with tramadol at its maximum dose. Isobolographic analysis demonstrated that the experimentally determined ED50 values (Zexp) for both combinations were significantly lower than their corresponding theoretical additive values (Zadd), indicating synergistic interactions. Specifically, the haloperidol + buprenorphine combination yielded a Zadd of 27.6 ± 5.5 and a Zexp of 5.47 ± 1.2, whereas the haloperidol + tramadol combination exhibited a Zadd of 4987.68 ± 651.5 and a Zexp of 1678.23 ± 89.8. Among the combinations evaluated, haloperidol produced a greater potentiation of antinociception when combined with buprenorphine than with tramadol. These findings demonstrate that haloperidol enhances the antinociceptive effects of both opioid analgesics through synergistic interactions, with the strongest effect observed in combination with buprenorphine. Such combinations may represent

promising pharmacological strategies for the management of chronic pain conditions, including cancer-related pain and pain associated with depressive disorders.

Disclosures: M. Deciga-Campos: None. **J. Lomeli:** None. **R. Ventura-Martinez:** None. **M. Rodríguez-Caratachea:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.09/BB22

Topic: E.01. Somatosensation – Pain and Itch

Support: VCU Quest grant

Title: Behavioral depression induced by dental pain in mice and its resistance to analgesics

Authors: *H. F. FILIPPINI[1,2], S. S. NEGUS[3,1], K. TAYLOR[3,1];
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Abstract: Acute dental pain contributes to approximately 10% of opioid analgesic prescriptions in the U.S., highlighting a critical need for safer, non-opioid alternatives. This study supports the NIH HEAL initiative by developing a preclinical model to investigate behavioral depression as one class of behavioral signs caused by dental pain, enabling future discovery of novel analgesics. This study had two aims: 1. Assess the depression of locomotor activity and oral activity and the stimulation of postural hunching and grimace as pain-related behavioral endpoints produced by a set of dental pain manipulations. 2. Evaluate the effectiveness of ketoprofen (NSAID) and morphine (opioid) to alleviate these behavioral effects. Male and female ICR mice (8 weeks old; n=12/group) were subjected to one of the four dental pain manipulations: (1) Control - anesthesia only, (2) Open -pulp exposure, (3) Closed-Sal - pulp exposure + insertion of saline-soaked point in the pulp + sealing, (4) Closed-CFA - pulp exposure + insertion of CFA-soaked point in the pulp + sealing. Locomotor activity (automated chamber) along with posture and facial grimace scores were assessed 6h after surgery. Additionally, retrieval and consumption of sunflower seeds were assessed after 24h to provide a measure of chewing required to crush the hull and extract the seed. For pharmacological studies, Closed-CFA mice received subcutaneous injections of vehicle, ketoprofen (1 or 10 mg/kg), or morphine (1, 3.2 and 5.6 mg/kg) immediately, 3 hours, and 5.5 hours post-surgery. Relative to the control treatment, dental-pain manipulations produced significant, graded depression of locomotion and seed consumption (Open<Closed-Sal<Closed-CFA) while increasing posture and grimace scores. Ketoprofen (10 mg/kg) and morphine (3.2 and 5.6mg/kg) significantly attenuated Closed-CFA-induced stimulation of posture, but neither drug alleviated any other Closed-CFA effects. This model demonstrates translational relevance by capturing multiple dimensions of dental pain. The limited efficacy of both ketoprofen and morphine underscores the

need for novel non-opioid analgesics capable of addressing the complex behavioral consequences of dental pain.

Disclosures: H.F. Filippini: None. **S.S. Negus:** None. **K. Taylor:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.10/BB23

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS131812
NIH/NIHGMS grant R35GM139430

Title: Pro-Resolving Mediators and their Function in Controlling Pain and Inflammation

Authors: *J. JI[1], Y. LI[2], S. BANG[2], R.-R. JI[2], C. SERHAN[1];
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Abstract: Acute inflammation is the body's protective response to tissue damage or infiltration by pathogens and is necessary for tissue repair post-injury. However, if unregulated, acute inflammation can become chronic, resulting in painful inflammatory diseases that significantly reduce quality of life. The termination of inflammation is an active process known as resolution, which is mediated by specialized pro-resolving mediators (SPMs) derived from long-chain polyunsaturated fatty acids (PUFAs). SPMs bind to specific G protein-coupled receptors (GPCRs) to mediate the actions of immune cells. The muscle-derived SPMs and their roles in resolving pain and inflammation are still of interest. To this end, we conducted solid phase extraction with liquid chromatography tandem mass spectrometry (LC-MS/MS) using muscle tissues near tibial bones from mice with and without bone fracture, a condition that causes severe inflammation and pain. We identified several SPMs, including resolvins and protectins. Compared to protectin D1 (PD1), protectin DX (PDX) is present at higher amounts in tibial bone fracture mice directly compared to wild-type mice. PDX displayed greater analgesic action than PD1, gabapentin, RvD5, MaR1, and DHA in the fracture model of postoperative pain. PDX promotes inflammation resolution via activation of GPR37 and macrophage efferocytosis. Thus, our findings identified PDX as a muscle-derived SPM that exhibits more potent analgesic actions than its family member PD1. We also hypothesize that PDX is produced at higher levels in injured mice to facilitate the resolution of inflammation and inflammation-associated pain. Future studies are needed to investigate PDX-mediated GPCR signaling.

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Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.11/BB24

Topic: E.01. Somatosensation – Pain and Itch

Title: Preliminary Evaluation of the Antinociceptive Effects of Mesquite (Prosopis glandulosa) Flower-Derived Honey in a Murine Formalin Model

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Abstract: Background: Pain is a complex and multifactorial phenomenon involving sensory, emotional, and cognitive components, often associated with inflammatory processes. Despite the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, their long-term use is limited by significant adverse effects. Honey has emerged as a natural product with antioxidant and anti-inflammatory properties; however, its biological activity varies according to botanical origin and geographical factors, which may influence its pharmacological effects. In this context, the antinociceptive potential of honey derived from *Prosopis glandulosa* (mesquite) flowers remains poorly characterized. Objective: To evaluate the antinociceptive effect of mesquite (*Prosopis glandulosa*) flower-derived honey in a murine formalin-induced pain model. Male mice were orally administered mesquite honey (100 mg/kg) or diclofenac (100 mg/kg). Methods: Nociceptive behavior was assessed using the formalin test, which comprises an early phase (1-10 min) associated with direct nociceptor activation and a late phase (15-60 min) related to inflammatory processes and central sensitization. Behavioral responses were compared with a vehicle-treated control group. Results: Both mesquite honey (100 mg/kg) and the reference drug diclofenac (100 mg/kg) significantly reduced nociceptive behavior during the late phase of the formalin test compared to the vehicle group ($p<0.05$). No significant differences were observed during the early phase among the tested compounds. These findings suggest that honey primarily modulates inflammatory-mediated nociception. Conclusion: Mesquite flower-derived honey exhibits significant antinociceptive activity in a murine model, particularly during the inflammatory phase of the formalin response, supporting its potential as a complementary therapeutic strategy for inflammatory pain management.

Disclosures: M.M. Hernández Herrera: None. **C. Alba-Betancourt:** None. **J.V. Espinosa:** None. **N.V. Vega Cabrera:** None. **C.R. Solorio Alvarado:** None. **F.B. Ramírez Montiel:** None. **O.A. Jaramillo-Morales:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.12/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Title: Interaction herb-drug: Tagetes lucida extract decreased the ketorolac antinociception in rats

Authors: *I. A. SOLIS GORTAREZ[1], G. E. ANGELES-LOPEZ[3], R. VENTURA-MARTINEZ[4], M. GONZÁLEZ TRUJANO[5], M. DECIGA-CAMPOS[2];
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Abstract: Inflammatory pain is a complex pathophysiological response mediated by pro-inflammatory substances that amplify nociceptive signaling. Nonsteroidal anti-inflammatory drugs, such as ketorolac, are commonly used for their treatment; however, the concomitant use of medicinal plants may modify the antinociceptive response. *Tagetes lucida* is a medicinal plant that is traditionally used to treat inflammatory pain. This study aimed to evaluate the antinociceptive pharmacological interaction between the aqueous extract of *Tagetes lucida* and ketorolac. The aqueous extract of *Tagetes lucida* was obtained by freeze-drying an infusion and characterized by HPLC. Antinociceptive activity was evaluated in the inflammatory pain model induced by intra-articular injection of 30% uric acid into the right hind limb, resulting in functional loss. The functionality was recorded every 15 min during the first hour and every 30 min thereafter, for a total evaluation period of 4 h. Pretreatment with ketorolac (0.56-10 mg/kg, p.o.) or *Tagetes lucida* (31-562 mg/kg, i.p.) produced a dose-dependent recovery of limb functionality after uric acid injection; at the maximum doses evaluated, ketorolac (10 mg/kg, 75.81%) showed greater effect than Tagetes lucida (562 mg/kg, 54.59%). Effective dose 50 (ED_{50}) was determined by the dose response curve of Tagetes lucida (402.64 ± 25.2 mg/kg) and ketorolac (2.55 ± 0.6 mg/kg); these values were used with the isobolographic method to propose four combinations in a 1:1 ratio using 50% effect level. The Zexp (270.3) value was higher than Zadd (202.5) and statistically different using Student's T-test. These findings suggest that *Tagetes lucida* decreased ketorolac's antinociceptive effect, suggesting a pharmacological antagonist. The co-administration of *Tagetes lucida* and ketorolac warrants further investigation to characterize the nature of the interaction and its potential impact on the management of inflammatory pain.

Disclosures: I.A. Solis Gortarez: None. **G.E. Angeles-Lopez:** None. **R. Ventura-Martinez:** None. **M. González Trujano:** None. **M. Deciga-Campos:** None.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.13/BB25

Topic: E.01. Somatosensation – Pain and Itch

Title: Genetic Identification and Pharmacological Validation of THIK-1 as a Chronic Pain Drug Target

Authors: *A.-P. KOIVISTO[1], N. JALAVA[3], E. SERKKOLA[2], W. HENNAH[2], K. AUVINEN[1], H. CHAPMAN[1], R. J. LUND[4];
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Abstract: There is a significant unmet need for more effective and safer pharmacological treatments for chronic pain. Using data from the UK Biobank, we identified several variants in KCNK13, the gene encoding the tandem-pore domain potassium channel THIK-1, as being associated with chronic and joint pain. THIK-1 is predominantly expressed in microglia, where it plays a central role in regulating the resting membrane potential and activation of the NLRP3. Importantly, selective THIK-1 inhibitors have recently been developed and are currently being evaluated in Phase 2 clinical trials. Based on this strong genetic, biological, and translational rationale, we hypothesized that THIK-1-dependent activation of the NLRP3 inflammasome in microglia contributes to osteoarthritis (OA)-related pain. To test this hypothesis, we synthesized a selective small-molecule THIK-1 inhibitor CVN293 and characterized its pharmacological properties and off-target activity. Analgesic efficacy was assessed in both the early and late phases of the rat MIA model of OA pain in two independent laboratories. PK, along with plasma and brain exposure of CVN293, were evaluated using terminal samples collected from rats included in the efficacy study. Additionally, the analgesic potential of CVN293 was examined in a hyperalgesic priming model. NLRP3 inhibitor MCC950 was used as a positive control in mice. In parallel, we examined the effects of THIK-1 inhibition using human iPSC-derived microglia. Proinflammatory cytokine release was quantified. We confirmed that CVN293 is a highly potent and selective inhibitor of both human and rodent THIK-1 channels. In vivo, CVN293 significantly reduced mechanical hypersensitivity in both the early and late phases of the MIA OA model. A robust PK-PD relationship was observed, linking analgesic efficacy to free drug concentrations in both plasma and brain. In addition, the NLRP3 inhibitor MCC950 attenuated mechanical pain in the hyperalgesic priming model. The THIK-1 inhibitor CVN293 also produced robust analgesic effects. Importantly, these findings provide the first evidence that selective THIK-1 inhibition attenuates both mechanical hypersensitivity and hyperalgesia in the MIA model of OA pain as well as in the hyperalgesic priming model. In vitro, CVN293 dose-dependently suppressed the release of proinflammatory cytokines from human microglia-like cells. Together, these results support THIK-1 as a novel target for the treatment of chronic inflammatory pain.

Disclosures: A. Koivisto: A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation. **N. Jalava:** A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation. **E. Serkkola:** A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation. **W. Hennah:** A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation. **K. Auvinen:** A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation. **H. Chapman:** A. Employment/Salary (full or part-time):; Orion Pharma Orion

Corporation. **R.J. Lund:** A. Employment/Salary (full or part-time):; Orion Pharma Orion Corporation.

Poster

PSTR314: Inflammatory Pain and Itch

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR314.14/BB26

Topic: E.01. Somatosensation – Pain and Itch

Support: CCCRP C025064

Title: Evaluation of JAK Inhibitors as Novel Analgesics for Burn Pain

Authors: *T. HICKMAN, A. FRIESENHAHN, T. GARZA, R. CHAVEZ, C. HINOJOSA-LABORDE, B. P. CHEPPUDIRA;
U.S. Army Inst. of Surgical Res., San Antonio, TX

Abstract: Introduction: Burn pain involves complex mechanisms that contribute to acute and chronic pain experiences. Current therapeutic options to manage burn pain include the use of opioid-based and non-steroidal anti-inflammatory drugs, which produce partial relief and are often associated with adverse side effects. Burn injury-induced cytokines play an important role in generating and maintaining burn pain, though underlying mechanisms are not fully understood. Cytokines interact directly and/or indirectly with the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling cascade. We hypothesized that JAK inhibitors reduce pain behaviors in an animal model of burn pain by attenuating proinflammatory mediators. **Materials and Methods:** Adult male Sprague-Dawley rats were deeply anesthetized and thermal injury (TI) induced by placing a pre-heated (100 °C) soldering tip on the mid-plantar surface of the right hind paw for 30 s. Baseline mechanical allodynia (MA) and thermal hyperalgesia (TH) were measured prior to TI on day 0. On day 7 post-injury, one set of rats (TI n=5; sham n=5) were humanely euthanized and spinal cord tissue was harvested. For behavioral experiments, MA and TH were measured on day 7 and animals were subcutaneously administered 5, 10, or 30 mg/kg Baricitinib (n=5 per dose), vehicle (n=5), 5 or 10 mg/kg Upadacitinib (n=5 per dose), vehicle (n=5), and morphine (n=5). MA and TH were assessed 1 hour, 3 hours, and 5 hours-post treatment on day 7. Animals were then humanely euthanized and spinal cord tissue harvested. Expression of JAK1 and JAK2 receptors from spinal cord tissue were studied using ProteinSimple Jess. **Results:** Activation of JAK1 [1.6-fold increase vs non-injured sham] and JAK2 [1.4-fold increase vs non-injured sham] receptors was observed in the spinal cord of rats with TI. However, Baricitinib had no effect on pain behavior in the TI model. 10 mg/kg Upadacitinib met our clinical threshold of ≥30% decrease in MA and TH behavior from vehicle, though no significant change in JAK1 expression was observed. **Conclusion:** To date, our pilot experiments revealed that burn injury activates JAK1 and JAK2 receptors in the spinal cord of rats with TI. Upadacitinib also may attenuate pain behaviors. These initial results

implicate that JAK-STAT signaling in burn pain mechanisms. Evaluation of analgesic mechanisms of JAK inhibitors is ongoing.

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Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.01/BB27

Topic: E.03. The Chemical Senses

Support: NICHD intramural grant

Title: Anatomical characterization reveals separate palp-mediated and antennal olfactory pathways in the locust brain

Authors: *Z. N. ALDWORTH, K. SUN, M. A. STOPFER;
NIH-NICHD, Bethesda, MD

Abstract: Olfaction in locusts offers a useful model for understanding how the brain encodes environmental information. While previous studies of olfaction in locusts have focused mainly on the antennal pathway, most insects including locusts possess olfactory receptors on their palps, and recent evidence suggests they contribute to olfactory processing. The palps thus initiate a second olfactory pathway whose neural architecture and sensory functions remain largely unexplored. Here, we used anterograde and retrograde dye fills, intracellular labeling, scanning electron microscopy, and confocal imaging to characterize the palp chemosensory system in the locust *Schistocerca americana*, tracing projections from peripheral sensilla to higher-order brain regions. We found that sensory input from the palps projects to two distinct regions: the gnathal ganglion and the glomerular lobe of the cerebral ganglion. The gnathal ganglion integrates gustatory input from multiple head appendages, whereas the glomerular lobe, previously considered a gustatory or multimodal structure, receives direct input exclusively from olfactory sensory neurons on the palps, marking it as an olfactory structure. Neurons projecting from the glomerular lobe then innervate the accessory calyx of the mushroom body, defining a pathway from the palps to a higher-order olfactory processing center. Comparison with the well-characterized antennal olfactory pathway shows that the two systems remain anatomically segregated through at least third-order neurons. These results provide the first comprehensive anatomical characterization of a distinct palp-based olfactory pathway in the locust brain, and revise the functional interpretation of the glomerular lobe and accessory calyx, suggesting they participate in olfactory rather than gustatory processing. Our results also establish a framework for comparative functional studies of antennal and palp-based olfactory coding.

Disclosures: Z.N. Aldworth: None. **K. Sun:** None. **M.A. Stopfer:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.02/BB28

Topic: E.03. The Chemical Senses

Support: NIH Grant R35 GM133209

Title: Tools for studying enzyme jhamt expression and function in Drosophila

Authors: *A. PACRIN, K. MENUZ;
Univ. of Connecticut, Storrs, CT

Abstract: Juvenile Hormone (JH) is a sesquiterpenoid hormone known for its roles in controlling the development of insect larvae and in regulating reproduction in adult insects. JH is known to be synthesized and secreted by the corpora allata (CA), but snRNASeq data from the Fly Cell Atlas suggest that JH may be synthesized in the antenna due to its expression of jhamt, a key JH synthesis enzyme. Here, we characterize several new and previously developed tools for studying jhamt expression and function. First, we found that previously used GAL4 and LexA reporter lines do not have a consistent expression pattern in the antenna; these patterns also differ from that of new knock-in jhamt$^{T2A\text{-}LexA}$ and jhamt$^{T2A\text{-}GAL4}$ lines that we developed. Using our new jhamt reporter lines, we demonstrate that jhamt is expressed in non-neuronal cells of the antenna, including those that enwrap pheromone-sensing olfactory neurons to regulate mating behavior. Functionally, we find that an existing "GD" jhamt RNAi line does not affect mating behavior; however, it also does not reduce jhamt levels. A second jhamt "KK" RNAi line causes lethality, an unexpected observation considering that jhamt null mutations are viable. This suggests that this RNAi line has off target effects. Together, our work provides new tools to study jhamt expression and suggests that jhamt expression (and therefore function) may occur in more tissues than previously known.

Disclosures: A. Pacrin: None. **K. Menuz:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.03/BB29

Topic: E.03. The Chemical Senses

Support: NIH Grant R35 GM133209

Title: Identifying the Molecular Components that Generate the Transepithelial Potential in Insect Sensilla

Authors: *T. LONG, K. MENUZ;
Univ. of Connecticut, Storrs Mansfield, CT

Abstract: Insects rely on olfaction to navigate their environment, find food, locate mates, and avoid predators. Odorants are detected by sensory neurons housed in olfactory sensilla, the hair-like protrusions on the antenna. Olfactory sensilla share a similar structure with other types of insect sensilla that serve various sensory functions including taste, mechanosensation and hygrosensation. A key feature across all sensilla is a voltage difference between the sensillar lymph and hemolymph compartments, called the transepithelial potential (TEP), with the sensillar lymph being more positive. This potential is thought to drive cations into sensory neurons when receptors are activated, initiating neuronal firing. In many ways the TEP is similar to the endocochlear potential, which supports auditory transduction in the vertebrate cochlea. Like the endocochlear potential, the sensillar TEP is generated by support cells and likely involves potassium transport. However, the molecular basis of TEP generation remains entirely unknown. Here, we use the Drosophila olfactory system to systematically characterize and investigate the TEP. Using single sensillum electrophysiology, we demonstrate that the TEP varies across sensillum classes, while generally remaining stable across age and sex. Using an RNAi screen to identify candidate genes involved in TEP generation, we found two transporters, a V-type ATPase and an atypical SLC Unc93a ortholog, that are necessary for the TEP in olfactory sensilla. Finally, we demonstrate that loss of the TEP in support cells reduces odor-evoked neuronal responses, confirming that the TEP plays a critical role in insect sensillar neurophysiology.

Disclosures: T. Long: None. **K. Menuz:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.04/BB30

Topic: E.03. The Chemical Senses

Support: GM133209

Title: Cytochrome p450s in the Drosophila olfactory system

Authors: *S. BALLOU[1], K. MENUZ[2];
[1]Physiol. and Neurobio., [2]Physiol. & Neurobio., Univ. of Connecticut, Storrs, CT

Abstract: Enzymes in the large Cytochrome p450 (Cyp) superfamily have many well-known physiological roles including metabolism of clinical medications, detoxification of environmental toxins, and synthesis of steroid hormones and cholesterol. Interestingly, Cyps are

abundantly expressed in the olfactory tissues of animals ranging from insects to vertebrates. One putative function of Cyps is to metabolize odors to prevent prolonged signal activation. However, this theory has been difficult to test due to the paucity of information on their putative substrates and cellular localization in olfactory systems. Here, we used the *Drosophila* olfactory system to investigate the expression and function of Cyps. In *Drosophila*, different classes of olfactory sensilla (sensory hairs) contain 1-4 olfactory neurons that have stereotyped odor response profiles determined by their expression of particular odor receptors. To study the function of Cyps in *Drosophila* olfaction, we first selected 13 of the ~87 Cyps expressed in the antenna and generated novel transgenic reporter lines for each. Immunohistochemical analysis revealed that most Cyps are broadly expressed across the antenna, whereas a few are narrowly expressed. Comparison with cell-type markers revealed that most Cyps are expressed in one or more classes of sensillar support cells and epithelial cells; rarely are they found in neurons. For functional studies, we selected Cyp313a4 due to its narrow expression in the support cells of a specific olfactory sensilla class, the ac4 sensilla. Preliminary *in vivo* electrophysiological recordings suggest that the neuronal response to the odor phenylacetaldehyde, but not phenylacetic acid, is reduced upon loss-of-function of Cyp313a4. Together, this work will be the first map of Cyp expression in the olfactory system and one of the first studies showing a functional role for a Cyp in olfactory neuron responses.

Disclosures: S. Ballou: None. **K. Menuz:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.05/BB31

Topic: E.03. The Chemical Senses

Title: Cell-based assay development for predicting sensory adaptation to perfumery raw materials

Authors: *Y. ZORINA, D. COLOSIMO, Z. A. PETERLIN, C. DELAURA, B. SHARPE, D. ZAKHEIM, J. H. BRANN, P. PFISTER;
dsm-firmenich, New York, NY

Abstract: Sensory adaptation to odorants substantially influences fragrance perception and longevity, yet current evaluation methods primarily rely on human sensory panels, which are expensive and time consuming. To address this challenge, we developed three complementary cell-based assays to predict sensory adaptation to odorant molecules in vitro: (1) a high content imaging assay to quantify olfactory receptor internalization; (2) a kinetic assay to measure receptor mediated cAMP signaling over time; and (3) a live cell imaging assay to assess receptor activation and desensitization in response to repeated stimulation. Using human olfactory receptors and perfumery raw materials that cover multiple olfactory qualities, we observed distinct differences in receptor internalization and signaling changes over time, which correlated

with the degree of perceptual fading observed in human sensory testing. Additionally, treatment with ingredient mixtures revealed modulatory effects on adaptation, highlighting the assays' versatility for fragrance optimization. This scalable approach provides mechanistic insight into olfactory adaptation and offers a practical tool for ingredient selection, enabling more efficient design of fragrances with tailored profiles.

Disclosures: Y. Zorina: A. Employment/Salary (full or part-time):; dsm-firmenich. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent. **D. Colosimo:** A. Employment/Salary (full or part-time):; dsm-firmenich. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); dsm-firmenich. **Z.A. Peterlin:** A. Employment/Salary (full or part-time):; dsm-firmenich. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent. **C. DeLaura:** A. Employment/Salary (full or part-time):; dsm-firmenich. **B. Sharpe:** A. Employment/Salary (full or part-time):; dsm-firmenich. **D. Zakheim:** A. Employment/Salary (full or part-time):; dsm-firmenich. **J.H. Brann:** A. Employment/Salary (full or part-time):; dsm-firmenich. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent. **P. Pfister:** A. Employment/Salary (full or part-time):; dsm-firmenich. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.06/BB32

Topic: E.03. The Chemical Senses

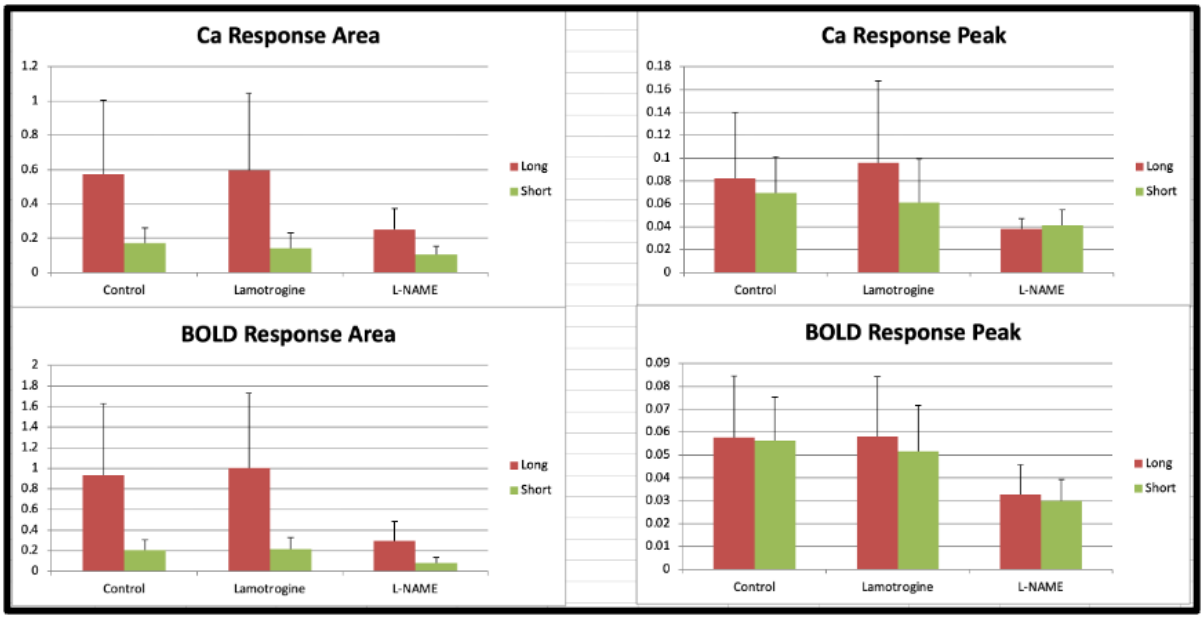
Support: NIH R01 MH-067528
NIH P30 NS-52519

Title: Dissecting neurovascular coupling of odor-evoked responses in the olfactory bulb: Interventions with lamotrigine and L-NAME

Authors: *J. V. VERHAGEN[1,2,3,4], K. L. BAKER[2], F. HYDER[5,3,4], B. G. SANGANAHALLI[3,4], P. HERMAN[6,4];
[1]Yale Sch. of Med., New Haven, CT; [2]The John B. Pierce Lab., New Haven, CT; [3]Radiology and Biomed. Imaging, [4]Yale Biomed. Imaging Inst., [5]Biomed. Engin., Yale Univ., New Haven, CT; [6]Radiology and Biomed. Imaging, Yale Univ. Sch. of Med., New Haven, CT

Abstract: To investigate neurovascular coupling embedded within the BOLD signal, we combined fMRI with optical calcium imaging of the rat olfactory bulb (OB) [1] and by pharmacological interventions we disrupted the neurovascular coupling[2]. In control conditions,

we found that OB BOLD odor responses were similar to presynaptic calcium dye responses. To assess postsynaptic contributions to BOLD, we tested the effects of decoupling pre- from postsynaptic glomerular activity using Na^+ channel blocker lamotrigine, expecting this would neither affect presynaptic calcium responses nor BOLD responses. We also hypothesized that reducing odor-evoked hyperemia by NOS inhibitor L-NAME would only reduce BOLD responses. **APPROACH:** We performed simultaneous optical imaging and fMRI in mice expressing Ca^{2+} indicator in the presynaptic terminals of the OB (B6 OMP-GCaMP6f). Mice received a cranial window and were imaged a week later under ketamine-dexdomitor anesthesia. BOLD was measured by GE-EPI fMRI (0.4x0.4x0.4mm voxels) with 14mm surface transceiver coil in a 11.7T Bruker scanner. Fluorescence microscopy was performed with a custom MR-compatible macroscope (3x4mm FOV) [3]. Stimuli were 20% methyl valerate of long (30 sec) or short (5 sec) duration. During control conditions the mice (n=9) received 3-5 trials with these stimuli. Next, they received lamotrigine (25mg/kg i.p.) 40 min before recording the same 3-5 stimulus repetitions. Days after recovery the same experiment was performed in 5 mice using L-NAME (30mg/kg i.v.) 5-10 min before first recording. **RESULTS:** Presynaptic Ca^{2+} responses were not affected by the Na^+ channel blocker but were reduced by NOS inhibition. We found similar effects of the treatments on the BOLD signal, with no effect by lamotrigine, and clear reduction by L-NAME. **CONCLUSIONS:** The concordant effects of NOS inhibition on presynaptic Ca2+ and BOLD responses, coupled with the absence of lamotrigine effects, demonstrate that olfactory bulb BOLD signals predominantly reflect presynaptic glomerular activity and its nitric oxide-dependent neurovascular coupling.



Disclosures: J.V. Verhagen: None. **K.L. Baker:** None. **F. Hyder:** A. Employment/Salary (full or part-time):; founder of InnovaCyclics, a biotech startup developing NextGen MRI contrast agents.. **B.G. Sanganahalli:** None. **P. Herman:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.07/CC1

Topic: E.03. The Chemical Senses

Support: Western Michigan University

Title: Assessing Olfactory Neuron Degeneration and Regeneration Following Chemical Ablation in Zebrafish

Authors: *B. A. WALLI[1], W. COLEMAN[3], C. A. BYRD-JACOBS[2];
[1]Biol. Sci., [2]Dept Biolog Sci., Western Michigan Univ., Kalamazoo, MI; [3]Western Michigan Univ. Sch. of Med., Kalamazoo, MI

Abstract: Zebrafish are a fitting model for studying neuronal damage and recovery, due to their impressive regenerative ability. Previous studies have shown that the administration of detergent to the nose of the zebrafish damages primarily the ciliated olfactory sensory neurons (OSNs) that mediate perception of social cues, with retention of microvillous OSNs involved in food perception. This study examined the effect of a second detergent exposure, to determine if microvillous OSNs are spared because they reside below the ciliary mat or they possess inherent neuroprotective mechanisms. Adult Zebrafish were anesthetized, and Triton X-100 was dispensed into the right nostril. For morphological analysis, the left nostril was untreated and served as an internal control, and for behavior experiments, the left nostril was also treated with Triton X-100. Animals received one or two detergent applications, the second dose occurring 24 hours following the first. For morphology, rosettes were dissected 24 hours after treatment, sectioned, and labeled with monoclonal anti-HuC/HuD to identify all OSNs. Optical density (OD) of labeling in the sensory epithelium was measured, and percent difference between right and left olfactory organs was compared. To test behavioral responses, amino acid-evoked movement was examined via motion-tracking software at baseline and across four time points over 7 days. Baseline fish moved an average of 2735 mm more during the 30 seconds after the amino acid addition. Following the second detergent treatment, fish moved 1279 mm less after addition of the amino acid and then by day 3, they moved 3883 mm more in response to the odorant. Fish showed significantly reduced responses following the second treatment, with behavioral recovery back to baseline by day 3. A significant reduction in anti-HuC/HuD labeling was observed in the 2x detergent-treated group ($P=0.031$), showing that there is a substantial loss of total OSNs in the sensory epithelium, even more so than when compared to the 1x-treated group. This suggests that more neurons are affected following two treatments, pointing to the possibility of microvillus OSNs degenerating with the ciliated OSNs. The behavioral response further supports the hypothesis that microvillous OSNs are lost following two treatments, as a loss of response to amino acids was seen 24 hours after the second treatment, but not after the first treatment. The current data suggests that microvillous OSNs succumb to a second treatment, but further exploration will include labeling for specific OSN cell types to help us better define differential degeneration and regeneration effects following chemical ablation.

Disclosures: B.A. Walli: None. **W. Coleman:** None. **C.A. Byrd-Jacobs:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.08/CC2

Topic: E.03. The Chemical Senses

Title: Expanding optical methods in olfactory bulb with prism and voltage imaging

Authors: *T. REIZIS[1], J. V. GILL[2], S. TUCKER[3], S. SHOHAM[4], D. RINBERG[5];
[1]Biomed. Engin., New York University, Tandon Sch. of Engin., New York, NY; [2]Inst. for Translational Neurosci., NYU Grossman Sch. of Med., New York, NY; [3]New York Univ., Brooklyn, NY; [4]NYU Grossman school of medicine, New York, NY; [5]Neurosci. Inst., NYU Neurosci. Inst., New York, NY

Abstract: In response to an odor, the glomerular layer of the olfactory bulb (OB) generates a spatiotemporal code containing all perceptually relevant dimensions. Glomeruli synapse onto the mitral/tufted cell (MTC) layer as the only secondary feedforward processing step before the signal is relayed to cortical areas. Therefore, gaining experimental access to the maximum number of glomeruli and to the precise dynamics of mitral/tufted cells in vivo is key to answering fundamental questions of olfactory processing.
The mouse OB is typically studied using calcium indicators imaged over the dorsal surface, however the glomerular and MTC layers extend medially and laterally, obscured from optical access. The raw number of experimentally accessible glomeruli is highly consequential to unraveling the olfactory code, as they provide the basis for probing how perceptual odor space is represented within their patterns of activation. To address this, we developed a surgical method to chronically implant a 2mm mirrored right-angle prism and image the medial wall of OB. The prism is bonded to a cranial window with optical adhesive, allowing for a stable implant that yields high imaging fidelity over several months of imaging experiments under single and multiphoton illumination. The preparation expands optical access by ~3.5 fold, adding over ~250 additional glomeruli to odor imaging datasets. This technique can allow for greater separability of odors with similar dorsal representations, and a powerful means of probing the basis of mixture representations. The preparation was further validated to ensure that unilateral bulbectomized mice maintain normative dorsal odor responses, as compared to standard cranial window preparations.
The greater obstacle to optical interrogation of MTCs is limited temporal resolution, due to the long decay coefficient of calcium. To improve future explorations of mitral cell functional organization, such as lateral and feedback dynamics, we have been validating recent genetically encoded voltage indicator (GEVI) constructs for use in OB. Using the FORCE1s GEVI (St. Pierre lab) in the MTC layer, we have optically resolved individual action potentials as well as sniff-locked subthreshold oscillations in MTC membrane potential.

Disclosures: T. Reizis: None. **J.V. Gill:** None. **S. Tucker:** None. **S. Shoham:** None. **D. Rinberg:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.09/CC3

Topic: E.03. The Chemical Senses

Support: DAE, Govt. of India. Project No RTI 4007
NIH Grant R21 MH099798

Title: Sensory neuron development is associated with differential ER stress-like state and specialized ER chaperones.

Authors: *G. DEVAKINANDAN, A. DANI;
Tata Inst. of Fundamental Res., Hyderabad, India

Abstract: In several vertebrates the vomeronasal or accessory olfactory system, specializes in detection of pheromones, kairomones and such chemo-signals that elicit innate stereotyped behaviors. The peripheral vomeronasal organ (VNO), has evolved an elaborate molecular organization, with major classes of G-protein coupled receptors (GPCR) being expressed in spatially segregated sensory neurons within the neuroepithelium. Because these neurons continuously regenerate and differentiate throughout the organism's lifespan, the VNO serves as an ideal model for studying both the neurobiology of innate behaviors and lifelong neuronal diversification. Using single-cell and comparative transcriptomics, we found that mature, V2R-expressing Gαo-subtype neurons significantly upregulate genes and proteins associated with the endoplasmic reticulum (ER). Notably, these Gαo neurons exhibit a hypertrophic cubic ER membrane ultrastructure indicative of an ER-stress-like state. This distinct cell-biological divergence prompted us to investigate Gαo-specific upregulated genes. Here, we characterize the molecular and functional roles of mouse *Cnpy1*, identifying it as a component of a VNO sensory-neuron-specific ER chaperone complex essential for Gαo neuron signaling and survival.

Disclosures: G. Devakinandan: None. **A. Dani:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.10/CC4

Topic: E.03. The Chemical Senses

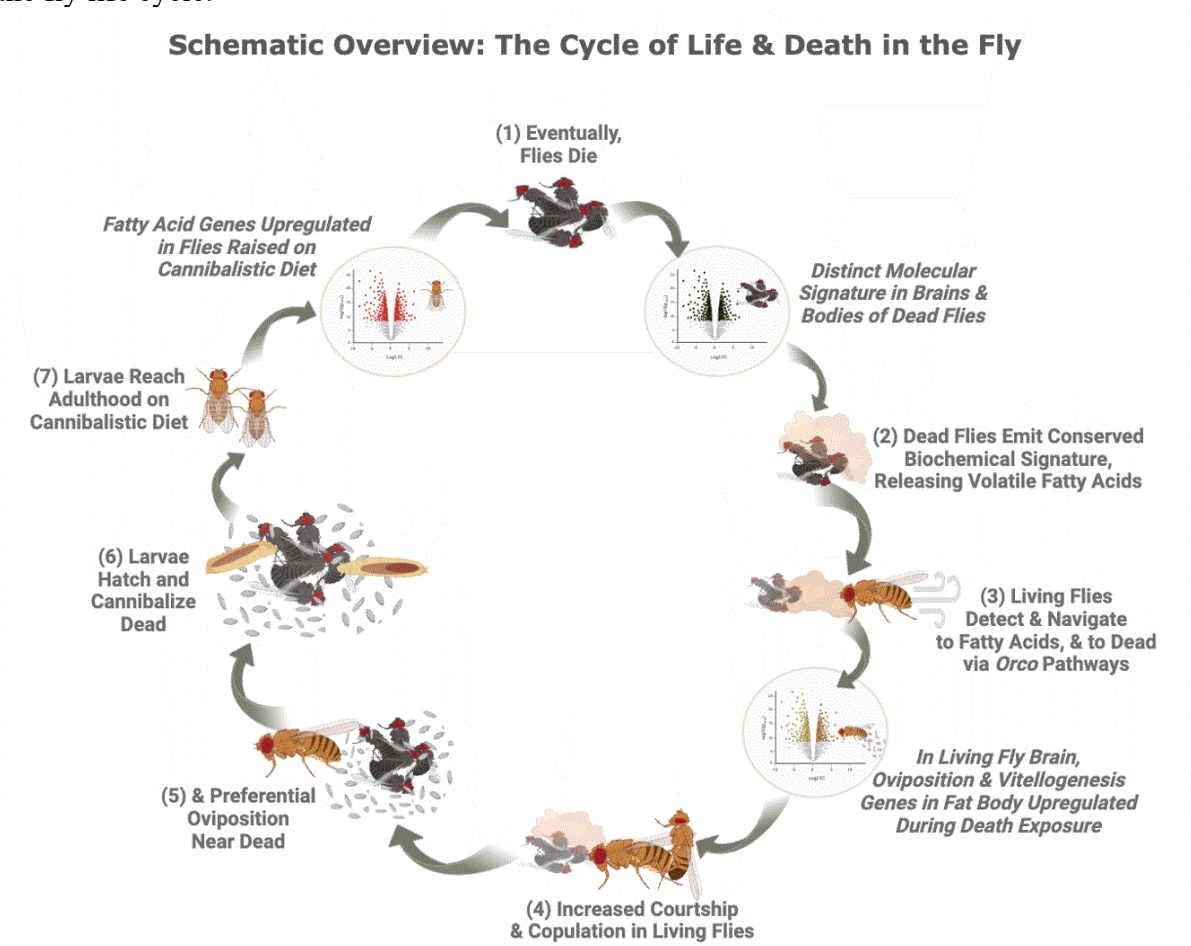
Support: NIH GR123040
Annie Le Fellowship
Gruber Science Fellowship

Title: Death as a Conserved Sensory Signal

Authors: *E. J. SIFF[1], F. MENGES[5,2], G. SANTANA[8], G. TALROSS[6,9], T. EMONET[3], F. MARION-POLL[7,10], J. R. CARLSON[4];
[2]Biophysical Chem., [3]Mol. Cell. and developmental Biol., [4]MCDB, [1]Yale Univ., New Haven, CT; [5]Orange, CT, ; [6]Rochester, NY, ; [7]Gif-sur-Yvette, ; [8]Yale Univ. Interdepartmental Neurosci. Program, New Haven, CT, ; [9]Med., Univ. of Rochester, Rochester, NY; [10]Egce-ideev, Paris-Saclay, AgroParisTech, Gif-sur-Yvette, France

Abstract: Death as a Conserved Sensory Signal
Animals routinely encounter the dead of their own kind. Yet, how nervous systems detect and respond to death remains poorly understood. Here, we integrate behavioral, chemical, and molecular analyses to characterize death as a sensory stimulus in *Drosophila* and to examine its consequences across generations.
Using GC-MS, we found that, across six species, dead flies emit a conserved post-mortem odor signature comprised of volatile fatty acids. This death signature is sufficient to guide navigation and oviposition decisions. Behavioral assays demonstrated that living flies detect these post-mortem cues through olfactory pathways, preferentially navigating toward and laying eggs near dead kin. When larvae hatch, they consume the corpses, providing an ecological explanation for why attraction to death may be adaptive.Exposure to dead flies altered adult reproductive behavior, increasing courtship and copulation, and induced coordinated transcriptional responses in living fly brains. RNA sequencing of exposed adults revealed upregulation of genes associated with oviposition, vitellogenesis, metabolism, and sensory processing, linking sensory detection of death to reproductive physiology.
To determine the developmental consequences of corpse consumption, larvae were reared to adulthood on standard fly food, a mixed diet containing fly food and dead kin (corpses), or corpse-only diet. Corpses alone were sufficient to support complete development to adulthood. However, corpse-only development produced consistent behavioral, biochemical, physiological, and transcriptional deficits. Across multiple assays, flies formed a hierarchical continuum, in which the most nutritionally deprived flies were those raised on the corpse-only diet, and the most nutritionally enriched were those raised on the mixed diet. These results indicate that consuming the dead is not inherently harmful; the dead can act as a beneficial nutrient.
Finally, transcriptomic analyses revealed that, in addition to conserved biochemical cues, the dead possess a conserved molecular signature, across multiple modes of death.
Together, these findings support a cyclical model in which death generates conserved sensory cues that guide behavior, reproduction, and offspring placement. Those offspring subsequently exploit the dead as a developmental resource, altering their physiology, chemistry, and gene expression before eventually contributing to the next generation of post-mortem signals. Death therefore acts not merely as an endpoint, but as a recurring sensory and ecological component of

the fly life cycle.



Disclosures: E.J. Siff: None. **T. Emonet:** None. **J.R. Carlson:** None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.11/CC5

Topic: E.03. The Chemical Senses

Support: NSF Grant 2341202
NIH Grant GM103440

Title: Insulin signaling remodels Rab-dependent cargo trafficking in olfactory sensory neurons to tune feeding behavior

Authors: *D. MATHEW;
Univ. of Nevada, Reno, Reno, NV

Abstract: An individual's metabolic state influences odor-guided food seeking across both short (e.g., hunger) and long (e.g., metabolic disease) timescales, yet how metabolic state remodels peripheral olfactory sensory neurons (OSNs) over short versus long timescales remains poorly understood. We found that insulin signaling dynamically regulates synaptic cargo trafficking in third-instar *Drosophila* larvae using OSN-specific RNAi, temporally restricted GAL80ts manipulations, OSN nuclear RNA-seq, immunocytochemistry, calcium imaging, and quantitative behavior. A 3-hr starvation protocol produced a selective OSN cargo-localization signature: Domeless (Dome), a leptin receptor homolog, decreased at OSN terminals, whereas Neuropeptide F (NPF), an NPY-like feeding signal, increased. Short-term (~3 hr) OSN-specific insulin receptor (InR) knockdown reproduced this Dome↓/NPF↑ signature and reduced Rab11, while a longer-term InR knockdown (>6 hr) reduced Rab5 and caused broader terminal cargo loss. OSN-specific transcriptomics independently identified vesicular trafficking as an insulin-sensitive pathway and Rab5/Rab11 as candidate mediators. Functional perturbation revealed a temporal division of labor: Rab11 dominant-negative expression reproduced the acute starvation/InR phenotype, whereas Rab5 dominant-negative expression reproduced the prolonged InR phenotype, including terminal cargo loss and abnormal Dome accumulation in axon shafts. These trafficking changes had behavioral and physiological consequences. Reducing Dome in OSNs increased attraction to the food odor pentyl acetate, increased feeding, increased larval weight, and increased buoyancy, a proxy for fat accumulation. Further pathway analysis indicated that FOXO, a transcription factor downstream of insulin signaling, primarily affected odor attraction, whereas STAT92e, a transcription factor downstream of the Dome/Jak/Stat pathway, increased NPF localization and altered feeding and physiology. Together, these findings identify a peripheral olfactory mechanism by which insulin/leptin signaling encodes metabolic-state duration through Rab-dependent cargo trafficking. We propose that Rab11 supports short-term hunger-like OSN remodeling, whereas Rab5 maintains longer-term cargo organization, providing a cellular framework for how short- and long-term metabolic signals differentially reshape sensory neurons.

Disclosures: D. Mathew: None.

Poster

PSTR315: Olfaction: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR315.12/CC6

Topic: E.03. The Chemical Senses

Support: NIDCD R01 DC013553
NINDS UF1 NS108213
Helen Hay Whitney PG013009
St Jude Children's Research Hospital

Title: Olfactory GPCR response properties explain nonlinear modulation in odor mixture coding

Authors: ***L. XU**[1], W. LI[1], S. J. FIRESTEIN[2], E. M. C. HILLMAN[1];
[1]Imaging Sci., St Jude Children's Res. Hosp., Memphis, TN; [2]Dept Biol., Columbia Univ., New york, NY

Abstract: Peripheral olfactory coding is shaped not only by odorant identity and concentration, but also by interactions between odor components. Here, we used methyl dihydrojasmonate (MDJ), a common perfume additive favored for its 'odor enhancing' properties as a tool to examine mixture interactions in the mouse olfactory epithelium. We used Swept Confocally Aligned Planar Excitation (SCAPE) microscopy to record the activity of olfactory sensory neurons (OSNs) within the intact olfactory epithelium of OMP-GCaMP mice. Odor-evoked calcium activity was extracted from large populations of OSNs, for repeated olfactory stimuli corresponding to a range of concentrations of primary odors, binary combinations of odors, and with and without MDJ.
MDJ produced only weak agonist responses by itself, but strongly modulated OSN responses to multiple primary odors, including citral, acetophenone, octenyl acetate, and linalool. Both positive and negative modulation was observed, with MDJ inhibiting responses in some OSNs while enhancing responses in others.
Importantly, our analysis enabled characterization of dose response curves of individual OSNs to specific ligands, revealing diverse response profiles across OSN subpopulations. Noting that each mature OSN expresses a single dominant G-protein coupled receptor (GPCR), these ligand-specific response profiles likely reflect differences in receptor-ligand interactions. Comparing responses with and without MDJ, we observed selective shifts in dose response curves that account for observations of enhancement or inhibition of responses at a given odor concentration, demonstrating that modulation effects reflect odor- and receptor-specific GPCR binding interactions rather than a global gain change. These insights suggest that multi-odor interactions could be predicted, at least in part, from the functional response properties observed for constituent odors. Our results further suggest that MDJ is an especially powerful modulator of functional GPCR response properties across broad receptor types.

Disclosures: L. Xu: None. **W. Li:** None. **S.J. Firestein:** None. **E.M.C. Hillman:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.01/CC7

Topic: E.07. Visual Sensory-Motor Processing

Title: Neural circuits for visual processing of conspecifics during Drosophila courtship

Authors: ***A. HAMID**[1], H. NOUSHAD[2], A. NERN[1], G. M. RUBIN[1], A. G. OTOPALIK[1];
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Abstract: Visually-guided pursuit of conspecifics is central to courtship in Drosophila. Males must orient toward and pursue a female, and continuously tune their visuomotor strategy in response to the female's movements. Prior studies demonstrated that LC10a visual projection neurons are responsive to fly-sized moving objects and required for pursuit. The retinotopic LC10a population projects from the optic lobe to the anterior optic tubercle (AOTU), an optic glomerulus in the central brain. Using the male whole-brain connectome, we find that postsynaptic AOTU neuron types receive input from different pools of LC10a neurons and inherit spatially distinct predicted receptive fields. This suggests that conspecific location and motion is differentially filtered across the AOTU population and transmitted to different brain regions to guide social action selection and navigation. Here, we present our ongoing investigation of the behavioral and neurophysiological functions of the AOTU population. Using a library of AOTU type-specific genetic driver lines, we measured male courtship pursuit, positioning, and song production during optogenetic silencing of individual AOTU types. Silencing several AOTU cell types disrupted multiple components of courtship-males failed to orient toward and maintain proximity to the female, and exhibited song production defects. We have also begun recording calcium and electrophysiological activity in different AOTU types in tethered male flies during presentation of reduced and virtual conspecific-like visual stimuli. Using these approaches, we are verifying their predicted receptive fields, determining how the AOTU neurons respond to conspecific motion, and characterizing under which virtual social and internal state conditions the different AOTU neurons are recruited. We observe diverse neurophysiological responses to these stimuli. Taken together, we aim to comprehensively describe visual processing in this AOTU layer and the social behavioral functions of these AOTU neuron types.

Disclosures: A. Hamid: None. **H. Noushad:** None. **A. Nern:** None. **G.M. Rubin:** None. **A.G. Otopalik:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.02/CC8

Topic: E.07. Visual Sensory-Motor Processing

Support: Duke Institute for Brain Sciences Fellowship

Title: Neural mechanisms of visually driven action selection in larval zebrafish

Authors: *Z. HE[1], R. MARRI[2], T. GAO[2], K. FOUKE[2], J. A. ATKINSON[2], C. FEHRMAN[2], M. LORING[2], E. A. NAUMANN[2];
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Abstract: To successfully navigate natural visual environments, the vertebrate brain must selectively transform the most relevant sensory cues into appropriate actions. Visual processing and action selection in mammals involve cortical and subcortical brain-scale networks. However, the simultaneous recording of multi-region, single-cell level neural circuit activity and behaviors poses a significant challenge. Here, we investigated the brain-scale neural circuits underlying visually driven action selection in the optically accessible larval zebrafish. In the wild, zebrafish hunt visible prey objects (hunting) while stabilizing their position to counteract being swept away by water currents, using the visually driven optomotor response (OMR). To investigate how larval zebrafish perform this action selection, we conducted high-speed behavioral tracking while simultaneously presenting moving gratings and bright dots, simulating global motion induced by water flow and moving prey. Comprehensive characterization of swim bout dynamics and eye vergence demonstrates that dot stimuli trigger stereotypical hunting behavior and interrupt ongoing OMR. This action-selection bias towards hunting significantly reduces animal's response to global visual motion cues. Further, this extend of OMR suppression by the prey-like stimuli depends on behavioral history and competing stimulus salience. Using brain-wide 2-photon calcium imaging paired with behavioral tracking in head-fixed zebrafish, we reveal parallel processing and mixed selectivity in grating- and dot-processing circuits. Dimensionality reduction method identifies neuron populations that reliably represent the visual stimulus and the action selection outcome. Finally, we used optogenetic stimulation to casually characterize the influence of dot responsive neurons activation to grating processing circuit. Together, our results demonstrate visual processing networks that parallelly represent competing sensory cues and selectively prioritize behaviorally relevant information to guide action selection. These findings provide insight into the neural principles for vertebrate brains to resolve sensory competition and generate adaptive behavior in complex environments.

Disclosures: Z. He: None. **R. Marri:** None. **T. Gao:** None. **K. Fouke:** None. **J.A. Atkinson:** None. **C. Fehrman:** None. **M. Loring:** None. **E.A. Naumann:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.03/CC9

Topic: E.07. Visual Sensory-Motor Processing

Support: The McDonnell Center for Systems Neuroscience SGP FY24

Title: Brain-wide circuits for competing prey processing in larval zebrafish

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Abstract: Animals often must choose one object for action while ignoring other simultaneously available stimuli. Prey hunting provides a natural setting for studying this problem. Larval zebrafish frequently encounter multiple prey and must orient toward and capture one selected prey item, the target, even when other prey are present. Using this model system, we asked how the brain represents this competition context, defined here as whether hunting occurs with a single prey item or with multiple competing prey. Behaviorally, competing prey reduced capture success and biased the fish's initial orienting turn, indicating disrupted target selection. Brain-wide calcium imaging revealed widespread suppression of neuronal activity evoked by the selected prey, with the strongest effects in the habenula and nucleus isthmi. Population analyses showed regional specialization: the optic tectum primarily encoded target location, whereas the nucleus isthmi and habenula encoded competition context, and habenula was the earliest predictor of behavioral outcome. Competition and outcome also reshaped inter-areal communication. Habenula ablation impaired hunting, weakened inter-areal communication, and disrupted competition-related representations, particularly in the nucleus isthmi. These results reveal a brain-wide circuit mechanism for selecting among competing stimuli and identify the habenula as a key node linking sensory competition to behavioral engagement.

Disclosures: S.I. Zhu: None. **M. Levendosky:** None. **M. Ryan:** None. **T. Tsai:** None. **G.J. Goodhill:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

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Topic: E.07. Visual Sensory-Motor Processing

Support: Natural Science Foundation of Beijing Municipality (IS23073)
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e R&D Program of Beijing Municipal Education Commission (1240030201)

Title: Single-neuron projectomes reveal distinct brain-wide projection architectures of the mouse superior colliculus

Authors: W.-W. WU[1], J. SU[2], H. CHENG[3], J. WANG[4], H. ZHAO[3], L.-Y. LI[1], ***Y.-T. LI**[3]; [1]Capital Med. Univ., Beijing, China; [2]Beijing Normal Univ., Beijing, China; [3]Chinese Inst. for Brain Research, Beijing, Beijing, China; [4]Peking Univ., Beijing, China

Abstract: Superior colliculus (SC) is a layered structure in the midbrain that is evolutionarily conserved across vertebrates. It plays a critical role in integrating sensory information and transforming it into actions during survival-related innate behaviors, such as defense and hunting. Although extensive studies have characterized its functions and underlying neural

circuits, the whole-brain output organization of the SC at single-neuron resolution remains largely unknown. Here, we combined sparse neuronal labeling, tissue clearing, and whole-brain axonal reconstruction to map the projections of individual SC neurons. Based on their projection patterns, we identified multiple projectome-defined neuronal types, each characterized by a distinct set of projection targets and collateral branching patterns. Projectome-defined types exhibited remarkable diversity in their long-range connectivity. Some types projected primarily within the ipsilateral hemisphere, whereas others established extensive contralateral connections, particularly with the contralateral SC and brainstem. Despite this diversity, individual neurons frequently collateralized across multiple anatomically and functionally distinct targets, linking thalamic, hypothalamic, midbrain, pontine, and medullary circuits. These projection patterns revealed distinct output channels associated with sensory relay, bilateral sensorimotor coordination, orienting and hunting behaviors, and defensive responses. Furthermore, neuronal types exhibited regionally biased distributions across SC layers and subregions, indicating a structured relationship between SC anatomy and downstream circuit engagement. Together, our results reveal an unexpectedly diverse and highly collateralized organization of SC output pathways. This dataset provides a comprehensive anatomical framework for understanding how the superior colliculus coordinates distributed brain-wide circuits and offers a foundation for dissecting the neural mechanisms through which SC outputs control innate behaviors.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

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Program #/Poster #: PSTR316.05/CC11

Topic: E.07. Visual Sensory-Motor Processing

Support: R15EY036226
P20GM144230
OIA2242771

Title: Concurrent, yet independent, ontogenetic change in zebrafish visual behaviors

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Abstract: For effective responsiveness and behavior, visual perception integrates multiple environmental characteristics and internal state. Two critical variables involved in light-induced behavior are the stimulus contrast (salience) and the perceived positive/negative correlation of the stimuli (valence). In larval zebrafish, it is established that when presented with a half-illuminated arena individuals will seek out the lighted portion, which is etiologically necessary for prey capture. However, while environment characteristics may persist, perceptional valence,

and associated behaviors, change throughout an individual's development. In fact, 90 dpf adult zebrafish behave with a reverse light preference compared to larval fish and will seek out the dark portions of a half-illuminated arena. However, while this behavioral flip is well established, when and how the neural mechanisms involved in this perception and behavioral change are unknown. Through longitudinal testing of groups from 7-90 dpf, we establish that this transformation occurs during at the larval-juvenile transition stage at 30 dpf. We further matched this behavior with a known light search behavior induced by the loss of illumination. Light search behavior in larval zebrafish persists as an individual bias for left or rightward turning following the loss of illumination. We hypothesized that the loss of a light search behavioral bias would be linked to a loss of individual preference for illuminated environments. Utilizing inter-individual comparisons between behaviors we demonstrate that both light-associated behaviors are transitioning at the same developmental stage, yet independently. We show that individuals at these developmental stages show dynamic morphologic and size differences, but this has no correlation with behavioral change. Moreover, we show that distinct changes in excitatory and inhibitory markers following behavioral transformations. Broadly, these results suggest that changes in perception are regulated by independent expression pattern changes across brain regions timed to allow for effective behavioral transition.

Disclosures: J. Starkey: None. **E. Horstick:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

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Topic: E.07. Visual Sensory-Motor Processing

Support: Cancer Research UK (CC2118)
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Title: Multiplexed coding of continuous sensorimotor information in the superior colliculus during visually guided pursuit

Authors: *Y. YANG[1], M. J. MOGLIE[1], A. POINTER[1], G. BIANCHINI[1], I. RAZAFINDRAHABA[2], X. CANO FERRER[1], M. F. IACARUSO[1];
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Abstract: Pursuing a moving target requires continuously translating target position and velocity into appropriate motor commands. Although the superior colliculus (SC) is known to play a key role in prey capture behaviours, how it transforms kinematic variables into flexible pursuit behaviour remains unclear. Here, we recorded 1,140 neurons from the SC of mice performing a closed-loop visually guided pursuit task, in which mice intercepted a moving dot on a

touchscreen for reward. We characterized the continues representation of task variable by the SC at single-neuron and population levels. Generalized additive models (GAMs) revealed that around 60% of neurons were modulated by at least one task variable, spanning a sensorimotor continuum—visual (egocentric prey location), motor (running speed, acceleration, heading, egocentric head angle), and other task related variables (line-of-sight, distance to prey). Using these tuning properties to form functional subpopulations, revealed that most of them, including those primarily tuned to motor variables, could distinguish initial stimulus location during detection (100 ms post-onset) and target velocity during approach (400 ms post-onset), indicating that visual and motor signals are broadly multiplexed across the SC population. At the population level, principal component analysis (PCA) revealed structured dynamics: the first five components captured 37.99% of variance, with some dimensions invariant across conditions and others tracking trajectory divergence across initial position and velocity conditions. Applying PCA to each functional subgroup recapitulated these whole-population dynamics with shifts in component rank, suggesting the population geometry reflects coordinated activity across heterogeneous subpopulations. Together, these findings reveal that SC contains subpopulations encoding task variables spanning the sensorimotor spectrum, providing a substrate for the continuous updating required during visually guided pursuit.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

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Program #/Poster #: PSTR316.07/CC13

Topic: E.07. Visual Sensory-Motor Processing

Support: Simons Foundation Grant SFI-AN-NC-SCN-00007276-04
NIH Grant R01NS121919
NIH Grant R01NS127305

Title: V1 activity during gaze shifts is temporally structured by encoding of newly sampled visual content

Authors: *J. SHIN[1], E. ABE[3], P. R. PARKER[4], D. MARTINS[5], C. M. NIELL[2];
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Abstract: Natural vision unfolds via active sampling, as movements of the eyes and head bring new information about the visual scene onto the retina while also generating motor signals. Because sensory and motor variables are tightly coupled during natural gaze shifts, it remains unclear how the visual content sampled by each movement shapes cortical activity. Previous

work showed that mouse V1 responds to gaze shifts with a structured temporal sequence, but whether this temporal sequence reflects the specific visual input sampled on each gaze shift remains unknown. We analyzed V1 recordings from freely moving mice (n = 8) together with eye tracking, head movement, and head mounted world camera video. For each gaze shift, we quantified visual change in the sampled image and related it to V1 responses. Visual change did not act as a uniform modulation of the post-gaze response. Instead, gaze shifts with larger image changes selectively amplified each neuron's response pattern, strengthening positive components and deepening negative components according to each cell's temporal profile. This temporal sequence encoded the specific content sampled on each gaze shift. Visual filters estimated from head-fixed responses predicted the relative timing of gaze shift responses when applied directly to freely moving movies, and at the population level, decoded V1 activity became aligned with the visual input sampled after each gaze shift, following the same temporal order as the response sequence. This temporal organization was not a uniform movement signal but remained anchored to each neuron's visual selectivity: receptive fields measured during freely moving gaze shifts retained spatial organization and resembled those measured under head-fixed conditions. These results suggest that gaze shifts are content-specific sampling events during natural vision. Rather than producing a uniform movement response, V1 represents the content brought into view by each gaze shift through a temporally structured response sequence anchored to each neuron's visual selectivity, linking visual selectivity measured under controlled conditions to temporally ordered cortical activity during active vision.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

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Program #/Poster #: PSTR316.08/CC14

Topic: E.07. Visual Sensory-Motor Processing

Title: Flexible Integration of Visual and Auditory Cues During Visuomotor Learning in Gerbils

Authors: *J. OLUSINA;
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Abstract: Animals integrate information across sensory modalities to guide adaptive motor behavior in dynamic environments. While the use of visual and auditory cues for spatial navigation is well documented, the neural mechanisms supporting visuomotor learning, and their vulnerability to sensory loss, remain poorly understood. We hypothesize that visually guided distance estimation relies on distributed circuits that flexibly incorporate visual and auditory information, such that the integration or loss of auditory signals alters both behavior and neural activity during visuospatial tasks.To test this, Mongolian gerbils were trained on an ethologically relevant jumping task requiring distance estimation from visual and/or auditory cues. Gerbils

used retinal image size, the visual angle subtended by the landing platform, as a prior to judge distance across a variable gap. We presented contextual auditory cues to determine how contextual auditory signals shape jumping behavior and cue weighting.We found that auditory contextual cues biased jumping behavior, suggesting flexible cross-modal cue integration during distance estimation. Ongoing work will pair this behavioral assay with recordings in the posterior parietal cortex (PPC), a region implicated in spatial and contextual visual processing, beginning with experiments that combine PPC suppression and noise-induced hearing loss to test how this region integrates visual and auditory signals and how that integration is reshaped when hearing is compromised. As part of this effort we also developed an open-source toolkit for implementing and analyzing gap-jumping experiments, which we are making freely available to lower barriers for other laboratories.This work advances understanding of how sensory and motor circuits coordinate for spatial navigation and how that integration is reshaped by sensory impairment, with implications for mitigating the behavioral consequences of hearing loss and for understanding multisensory deficits in neurodevelopmental disorders.

Disclosures: J. Olusina: None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.09/CC15

Topic: E.07. Visual Sensory-Motor Processing

Support: KAKENHI JP23H04975
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JST PREST JPMJPR22S6
AMED JP23wm0625001

Title: Dissociable cortical signatures of motor and sensory processing during self-generated head movements in marmosets

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Abstract: Primates must integrate visual changes caused by self-motion with those generated by external objects to support predictive motor control. However, how distributed cortical networks coordinate visual and motor signals during active self-motion remains unclear. To investigate the processing and integration of visual and motor information, we analyzed 96-channel electrocorticographic (ECoG) signals covering widespread left cortex, together with head-mounted inertial measurement unit (IMU) signals, in three freely behaving marmosets. The animals' behavior was recorded using multiple synchronized external cameras. Low-frequency

activity (1-30 Hz) revealed characteristic activation patterns, showing widespread cortical activation time-locked to movement. This activity first emerged in the prefrontal (A8) and premotor (A6) areas approximately 100 ms before movement onset, and then propagated to occipital, parietal, and temporal regions. In contrast, high-gamma activity (80-200 Hz) increased in a limited set of frontal, temporal, and parietal channels almost simultaneously shortly before movement onset. In addition, channels corresponding to V6, V3a, and neighboring areas exhibited a second activation peak following the initial peak. These two high-gamma components showed distinct properties. Comparison between onset- and offset-triggered averages revealed that the first peak was more pronounced in head-movement-onset-triggered activity, whereas the second peak was slightly more pronounced in head-movement-offset-triggered activity. The first peak depended on head-movement duration, persisting longer during large head movements than during short movements, further supporting its association with head motion. By contrast, the second peak was largely independent of movement duration. A similar analysis of low-frequency activity revealed that frontal cortical activity was more strongly related to movement, whereas activity across visual cortical areas showed a stronger relationship to visual input. Finally, both low-frequency and high-gamma activity in V1 were observed even under dark conditions (total darkness with active head movements). However, low-frequency activity was significantly reduced during dark-passive conditions, in which animals were passively moved in darkness. These findings indicate that V1 activity is modulated not only by visual input but also by active self-motion. Together, our results reveal frequency-specific and region-specific cortical dynamics that may support the integration of motor and visual information during natural behavior.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.10/Web Only

Topic: E.07. Visual Sensory-Motor Processing

Title: Inter-Individual Variability in Flanker Task Responses Following Breathing and Oculomotor Priming

Authors: *N. KINATTUVILAI[1], V. R. SHANKAR[2,1], J. PUNETHA[1], A. .[1], S. APRAMEYAN P.B.[1], S. SRIVIDHYA[1], S. A. MANEY[1];
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Abstract: Executive-control performance varies considerably between individuals, yet intervention studies typically focus on group-average responses. This study examined individual variability in Flanker-task performance following breathing and oculomotor priming. Trained

young adult athletes with no known cognitive or musculoskeletal conditions (N = 27, 6 F; aged 21.3 ± 1.8 years) completed control (CON), breathing regulation (BR), and breathing regulation plus oculomotor priming (BROC) conditions using a randomized Latin-square crossover design. All conditions included the control warm-up (2-min jog, 10 squats, and 10 walking lunges). BR added 2 min of guided 4:6 breathing, and BROC added 2 min of guided 4:6 breathing plus five oculomotor exercises lasting approximately 2.5 min. Conflict processing was assessed using a 60-trial Eriksen Flanker task. Interference cost (IC) was calculated as the difference between incongruent and congruent median reaction times derived from correct trials only. A smallest worthwhile change threshold of 12.36 ms (0.20 × pooled baseline SD) was selected a priori on distribution based approach. Participants were subsequently classified as positive responders, trivial responders, or adverse responders. Considerable inter-individual variability was evident across all conditions (CV range: 62-74%). Seventeen participants demonstrated reductions in interference cost following BROC, eight showed little meaningful change, and two demonstrated increased interference costs. Baseline interference cost was moderately associated with response magnitude (Spearman $\rho = -0.65$, $P<0.001$), indicating that participants with higher baseline interference costs generally experienced larger reductions following BROC. Leave-one-out sensitivity analyses demonstrated that the overall condition effect remained significant following removal of any participant (P range = $P<0.001$ to $P<0.01$). BROC reduces conflict-related slowing in most trained college athletes, with the largest benefits observed in participants who begin with higher interference costs. These findings indicate that baseline executive-control performance helps identify athletes most likely to respond to acute breathing and oculomotor priming.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

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Topic: E.07. Visual Sensory-Motor Processing

Support: NIH Grant 1F32MH134455-01

Title: Motor-generated and learned expectations differentially shape self-motion processing in primate vestibular cortex

Authors: *L. J. GÓMEZ[1], K. E. CULLEN[2];
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Abstract: Accurate self-motion perception depends on the brain's ability to distinguish expected from unexpected sensory input. In the vestibular system, one well-studied form of expectation

arises during self-generated movement, where a cerebellar-based internal model predicts the sensory consequences of active movement. When sensory feedback matches this prediction, vestibular responses are suppressed, a phenomenon known as reafference suppression. Reafference suppression has been well characterized in several subcortical vestibular structures, including the vestibular nuclei (VN) and ventral posterior lateral thalamus (VPL), through recordings obtained during natural movements (e.g., gaze shifts). The question remains, however, whether this motor-related suppression of expected vestibular input is preserved at the level of neocortex. Another key question is whether context-dependent self-motion processing in cortex is limited to reafference suppression or extends to expectations acquired through associative learning, in which passive motion becomes predictable through experience.To investigate these questions, we examined self-motion processing in the parieto-insular vestibular cortex (PIVC) of non-human primates, a major node in the vestibular cortical network that receives direct input from VPL. We hypothesized that PIVC inherits context-dependent encoding of natural movement from VPL, resulting in suppression of sensory responses during active movement. To test this hypothesis, we recorded activity from PIVC neurons using Neuropixels-NHP probes while animals experienced passive head-on-body rotations and generated active gaze shifts. Consistent with our hypothesis, PIVC neurons exhibited markedly weaker sensitivities during active than passive head movements (~40% reduction in sensitivity), indicating that reafference suppression during natural active movement is preserved in vestibular cortex. We then tested whether sensory responses are also suppressed when passive motion becomes expected through associative learning, in which monkeys were repeatedly exposed to a tone cue followed by stereotyped passive whole-body rotation. In contrast to the robust suppression observed during active self-generated movement, tone-predicted passive motion did not produce an overall decrease in vestibular sensitivity, but a subset showed altered response dynamics. Together, these findings suggest that PIVC participates in context-dependent self-motion processing, but that motor-generated expectations and learned sensory expectations shape cortical vestibular responses in distinct ways.

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Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

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Program #/Poster #: PSTR316.12/CC17

Topic: E.07. Visual Sensory-Motor Processing

Support: German Research Foundation (HE8329/2-1)
Baden-Württemberg Landesgraduiertenförderungsgesetz
International Max Planck Research School for the Mechanisms of Mental Function and Dysfunction

Title: Neural dynamics of predictive processing across the sensorimotor-association hierarchy using iEEG

Authors: *G. Y. IWAMA[1], N. BINISH[2], J. J. LIN[3], R. T. KNIGHT[4], R. F. HELFRICH[5];
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Abstract: Predictive context reduces uncertainty about upcoming events, but neural signatures of prediction vary substantially across cortical areas and frequency bands. This heterogeneity may reflect the hierarchical organization of cortex, where contextual information and sensory-motor responses are expressed differently across lower-level sensorimotor and higher-order association regions. Using intracranial recordings from human patients (N = 33) performing a predictive target detection task, we compared high-frequency activity (HFA; 70-150 Hz) and low-frequency power (8-30 Hz; alpha/beta) across predictive and random sequences. Target presentation elicited a well-established sensorimotor response profile, with stronger HFA increases and stronger beta suppression in lower-rank sensorimotor regions than in association cortex. Beyond this response-related pattern, predictive context revealed an additional hierarchy-dependent beta modulation: lower-rank regions showed stronger beta suppression, whereas higher-rank association regions showed a relative beta increase. This opposing pattern suggests that predictive context does not modulate beta activity uniformly across cortex, but may differentially reconfigure neural dynamics along the cortical hierarchy. More specifically, the results are consistent with the possibility that beta-band activity indexes different computations at different hierarchical levels, reflecting contextual maintenance or coordination in association cortex and altered beta-mediated organization of local activity in lower-level sensorimotor regions. To test this interpretation, we further examine beta phase-HFA amplitude coupling, asking whether predictive context changes the extent to which beta rhythms temporally organize local population activity across hierarchical levels. Together, these analyses aim to dissociate response-related dynamics from predictive modulations across the cortical hierarchy.

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Poster

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Program #/Poster #: PSTR316.13/CC18

Topic: E.07. Visual Sensory-Motor Processing
Rehabilitation Science New Student Award

Title: Effect of augmented sensory feedback on proximal and distal muscle coordination during upper limb reaching

Authors: *P. THAPA[1], J. CHENG[2], S. A. JAYASINGHE[3];
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Abstract: Muscle cocontraction contributes to joint stability and movement accuracy during upper limb reaching. Excessive cocontraction occurs during novel, cognitively demanding tasks, and impairs efficiency by increasing joint stiffness and reducing limb range of motion. Previous studies have shown that augmented sensory feedback can reduce abnormal muscle cocontraction in individuals with spasticity. However, it remains unclear whether the type of feedback differentially influences cocontraction at proximal and distal joints. This distinction is important because proximal (shoulder) and distal (elbow) muscles are involved in different aspects of control - postural control vs. precision control, respectively, and may respond differently to different sensory modalities. Determining whether augmented sensory feedback produces joint-specific effects is clinically important to develop a targeted intervention for proximal vs. distal spasticity and improve coordination between the joints. We recruited 11 neurotypical adults (age: 28.73 +/- years; 3.95; 7 females, 4 males) to complete a cognitively challenging reaching task on the Kinereach system using their dominant hand. We tested two types of feedback - visual feedback consisted of the change in cursor color from red to green as hand position error decreased relative to the correct target; auditory feedback consisted of a beeping tone that increased in frequency as hand position error decreased. We used surface electromyography to record electrical activity from the posterior deltoid, anterior deltoid, biceps, and triceps muscles. We hypothesized that augmented sensory feedback would differentially reduce cocontraction at the shoulder and elbow joints. Results of paired t tests showed no significant differences between auditory and visual feedback with respect to shoulder cocontraction ($p = 0.110$) and elbow cocontraction ($p = 0.593$). Contrary to our hypothesis, the type of sensory feedback did not differentially affect proximal and distal muscle cocontraction. These findings, based on our cognitively challenging task, suggest that upper limb joint cocontraction may be influenced to a larger extent by task demands than by the type of sensory feedback. Future work should investigate whether augmented feedback that directly reflects muscle activity (e.g., EMG biofeedback) may elicit joint-specific differences in cocontraction that were not observed with hand position error feedback.

Disclosures: P. Thapa: None. **J. Cheng:** None. **S.A. Jayasinghe:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.14/CC19

Topic: E.07. Visual Sensory-Motor Processing

Support: SNSF Ambizione 223402

Title: Sensorimotor integration as a behavioral correlate of sense of agency

Authors: *J. NIEUWENHUIS, S. MICERA, T. BERTONI;
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Abstract: Our sense of self relies on our ability to identify ourselves as independent agents. Sense of agency, the pre-reflexive feeling of generating our actions, is the cornerstone of such process, emerging from the congruency between motor commands and sensory feedback. Like sense of agency, closed-loop motor control relies on the constant integration of efferent commands and afferent feedback. Investigating this link would connect a core component of self-representation to a functionally relevant behaviour, yet this relationship has not been empirically tested. We hypothesized that the inference of self-causation underlies both sense of agency and sensorimotor integration. Sensory features congruent with motor commands are selectively gated for sensorimotor integration, leading to a sense of agency. To test this, we developed a visuomotor task that simultaneously manipulated sense of agency, by introducing temporal incongruency, and quantified sensorimotor integration, by introducing correctable spatial distortions in visual feedback and measuring the resulting compensation. We found that temporal incongruency similarly affected explicit agency ratings and the amount of sensorimotor integration, and the two were correlated even at fixed incongruency, suggesting a deeper link than mere co-occurrence. These results were captured by a Bayesian model where the brain infers self-causation probability from temporal incongruency, and uses such estimate to weight visual information during motor control. Using EEG frequency tagging, we found that visual feedback reaches motor areas more in congruent conditions, consistent with a congruency-driven gating mechanism. These results pave the way for a unified neurocomputational framework bridging sense of agency and motor control.

Disclosures: J. Nieuwenhuis: None. **S. Micera:** None. **T. Bertoni:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.15/CC20

Topic: E.07. Visual Sensory-Motor Processing

Support: FWO grant number G097422N)
KU Leuven grant C14/22/134

Title: Inactivation of area 45b during action observation induces widespread functional changes and impairs natural grasping

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Abstract: Observation of hand actions engages a distributed network of parietal, premotor, temporal and prefrontal areas in primates. In our previous functional MRI (fMRI) study, we showed that reversible inactivation of the anterior intraparietal sulcus (AIP) reduces activity in prefrontal area 45b during observation of grasping actions, indicating a causal influence of AIP on the prefrontal node of the action observation network. However, the role of area 45b within

the action observation network remains unknown. In the present study, we combined reversible muscimol inactivation of 45b with fMRI in awake rhesus macaques during the observation of grasping actions and control videos. Monkeys viewed videos of humans and monkeys grasping as well as phase-scrambled and static control stimuli in a block-design paradigm while maintaining fixation. To further assess the role of area 45b during natural grasping, we analyzed grasping performance in the free-moving animal using computer vision-based tools (DeepLabCut). Unilateral reversible inactivation of area 45b resulted in widespread changes in cortical activation during action observation, including reduced activations in surrounding prefrontal regions (e.g., area 45a), in ipsilateral parietal cortex and in superior temporal regions. Multivoxel pattern analysis further revealed a degradation of action-specific representations in prefrontal cortex and in the temporal areas aSTSf, MST and FST. Beyond its effect on the action observation network, muscimol injection in area 45b impaired the temporal aspects of contralateral hand performance during grasping and, under free-choice conditions, produced a complete shift toward use of the ipsilateral hand. These results suggest that area 45b is a crucial hub linking action observation to action selection. Rather than contributing solely to motor execution, 45b appears to be involved in large-scale fronto-parieto-temporal interactions that support the visual processing of others' actions and plays a key role in the selection of one's own actions during natural behavior.

Disclosures: S. Riva: None. **P. Janssen:** None. **A. Sepe:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.16/CC21

Topic: E.07. Visual Sensory-Motor Processing

Support: Natural Sciences and Engineering Research Council of Canada

Title: Attention Parses Objects into Action-Relevant Parts During Grasp Planning

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Abstract: Successful grasping depends on selecting object information relevant for upcoming hand actions. It has often been assumed that during grasping, visual attention is split into multiple foci near the intended contact points on an object, whereas during reaching and other non-grasping actions, attention is directed toward the object's center of mass. This attentional allocation selectively enhances processing of action-relevant features at the grasp points. However, the neural mechanisms underlying such action-dependent attentional modulation across space and time remain underexamined. The present study investigated how the features near the grasp points and the center of gravity of an object are neurally represented during

grasping compared to reaching. Specifically, we tested if neural representations of grasp point features differ systematically from other object features, and whether this distinction depends on the intention to grasp. Eighteen participants viewed and then grasped or reached for objects varying along several feature dimensions such as grasp point geometry (the shape near contact points), the color of the object's center, and object orientation (independent of hand orientation). We applied support vector machine (SVM) classifiers to event-related potentials recorded during object preview (-100-500 ms) to decode neural representations of each task feature. Classification accuracy for grasp point geometry was significantly higher during grasp than reach planning (234-332 ms). Likewise, object orientation, despite being dissociated from hand orientation, was decoded more accurately during grasps than reaches (308-371 ms). Contrary to a strict grasp-point selection account, center color remained robustly represented during grasp planning and to the same extent as during reach planning (50-350 ms). Together, our results suggest action-dependent attention does not split into spatial foci. Rather, grasp planning selectively represents action-relevant object parts. These findings illuminate how the brain flexibly allocates neural resources to support grasp planning, with implications for understanding the coupling between action and attention.

Disclosures: J. Jeong: None. **K. Telang:** None. **M. Niemeier:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.17/CC22

Topic: E.07. Visual Sensory-Motor Processing

Support: NSF/CAREER IIS-2143440

Title: Testing differential predictions of Bayesian Active Sensing and Free Energy Principle using a gaze-contingent active sensing task

Authors: *K. BLACK[1], L. COLAK[2], R. M. HAEFNER[3,4];
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Abstract: The Free Energy Principle (FEP) and Bayesian Decision Theory (BDT) are two prominent frameworks for modeling action selection under uncertainty. Recent work has discussed theoretical similarities and differences between the two (Gershman 2022). Here, we show that the two frameworks make divergent predictions about eye movement patterns in an active evidence integration task. We extend a previously established active sensing paradigm in which participants make multiple saccades to gather information before reporting a perceptual judgement (Chattoraj et al. 2021). Our extension adds a task-irrelevant cue dimension, generating predictions about where participants direct their gaze that differ in two ways between the frameworks. First, BDT predicts that gaze is driven purely by information gain over task-

relevant latent variables, whereas FEP predicts that gaze is additionally driven by information gain over task-irrelevant latent variables. Second, BDT predicts that eye movement patterns are unaffected by reward, whereas FEP predicts a systematic dependence on reward magnitude. Our simulations quantify both predictions and identify the parameter regimes under which the frameworks are distinguishable. Data collection is underway to test these predictions in human participants.

Disclosures: K. black: None. **L. Colak:** None. **R.M. Haefner:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.18/CC23

Topic: E.07. Visual Sensory-Motor Processing

Support: Generalitat Valenciana, CIDEGENT 2021/028
Ministery of Science, SPAIN (Plan Nacional, PID2023-153262NB-I00)
Generalitat Valenciana, ESGENT 07/025

Title: A fronto-collicular circuit for routing visual distractions into goal-dependent behavior

Authors: K. SONG[1], G. USSEGLIO[1], P. FEUGAS[1], S. MOROU[1], P. CUI[2], P. F. LE MERRE[3], T. FEMENÍA[4], I. LAZARIDIS[5], ***A. A. KARDAMAKIS**[1];
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Abstract: Salient visual stimuli do not always capture behaviour, yet the neural mechanisms determining whether sensory events are ignored or acted upon remain unclear. Using a freely moving visual distraction task, we found that responses to identical distractors ranged from robust orienting to complete neglect and were predicted by pre-existing behavioural state. Retinal inputs reliably signalled distractor onset in the superficial superior colliculus regardless of behavioural outcome, indicating that behavioural variability does not arise from sensory detection. In contrast, activity within the lateral intermediate superior colliculus (lSCi) scaled with distractor engagement, and causal manipulations identified lSCi excitability as a key determinant of distractor routing. Simultaneous recordings further revealed that frontal cortical activity preceding distractor onset predicts subsequent engagement, while optosilencing of fronto-collicular pathways reduces distractibility. Large-scale recordings suggest that frontal and sensory signals converge within collicular circuits to shape behavioural outcome. Together, these findings support a model in which frontal cortical state enables the transformation of saliency into orienting action.

Disclosures: K. Song: None. **G. Usseglio:** None. **P. Feugas:** None. **S. Morou:** None. **P. Cui:** None. **P.F. Le Merre:** None. **T. Femenía:** None. **I. Lazaridis:** None. **A.A. Kardamakis:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.19/CC24

Topic: E.07. Visual Sensory-Motor Processing

Support: HHMI
UPMC CMRF

Title: Neural Correlates of Ketamine-induced Dilation in Time Perception

Authors: *J. R. WATERS[1,2], B. MADEIRA[3], M. N. SHADLEN[4], S. SHUSHRUTH[5];
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Abstract: Time perception is critical to nearly all cognitive operations, including decision-making, memory, and action planning. Prior work has identified a number of neural correlates of time perception, including single neuron ramping activity and population dynamics that evolve systematically with elapsed time. However, the relationship between these correlates and subjective time estimation is unclear. The NMDA-antagonist ketamine is known to distort subjective time estimation. We investigated how these distortions are reflected in single-neuron and population dynamics in area LIP, a region strongly associated with interval timing.

We recorded neural activity from LIP in two male macaques performing a time-anticipation task during intravenous infusion of subanesthetic doses of ketamine guided by a pharmacokinetic model. In this task, monkeys made a saccade to a remembered location after a go-cue whose timing was drawn from a Weibull distribution. Monkeys learnt to anticipate the go-cue. This was reflected by reaction times (RT) that decreased as a function of the hazard rate of the distribution. Ketamine induced a dose-dependent flattening of this function in both monkeys (ketamine interaction term: Monkey 1: $p < .001$, Monkey 2: $p = .033$) — in other words, the monkeys responded as if less subjective time had elapsed than objective clock time. This is consistent with a dilation of internal time estimation.

Neural activity during the delay epoch was heterogeneous across neurons, including subsets of neurons that ramped up or down with anticipation. To isolate anticipation-related signals from sensory and motor responses, we fit a generalized linear model (GLM) to each neuron's spiking activity. Ketamine had bidirectional effects on isolated anticipation-related firing rates (FR), inducing an increase in some neurons and decrease in others (ΔFR: Median: 0.19 Hz, IQR: [-5.11, 2.67] Hz).

To characterize population-level time representation, we used PCA to identify neural trajectories through state space over a fixed delay epoch. Ketamine induced a dose dependent lengthening of these trajectories i.e., the dynamics representing the same time duration traversed a longer path (permutation test, both monkeys: $p \leq 0.001$). This lengthening provides a neural correlate of

ketamine induced dilation of subjective time observed in behavior. Our findings demonstrate that low-dose ketamine disrupts time estimation while systematically reshaping LIP population dynamics, providing a pharmacological framework for investigating how cortical activity supports timing behavior.

Disclosures: J.R. Waters: None. **B. Madeira:** None. **M.N. Shadlen:** None. **S. Shushruth:** None.

Poster

PSTR316: Sensorimotor Transformation: Behavior and Neuroprocessing

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR316.20/Web Only

Topic: E.07. Visual Sensory-Motor Processing

Title: Acute Effects of an Integrated Breathing and Oculomotor Warm-Up on Visual Search Performance in Trained Collegiate Athletes

Authors: *S. APRAMEYAN, PB[1], V. R. SHANKAR[2,1], J. PUNETHA[1], N. KINATTUVILAI[1], A. .[1], S. SRIVIDHYA[1], S. A. MANEY[1];
[1]Dept. of Sports and Exercise Sci., REVA Univ., Bengaluru, India; [2]Applied Physiol. and Kinesiology, Univ. of Florida, Gainesville, FL

Abstract: Athletes competing in open-skill environments rely on rapidly identifying relevant visual information and making timely decisions under constantly changing conditions. Brief breathing interventions and oculomotor activities have each been shown to influence attentional and visuomotor processes, yet whether combining these strategies acutely alters perceptual-attentional performance remains unknown. This study examined whether a brief integrated breathing and oculomotor warm-up influences visual search performance relevant to sport. Trained young adult athletes with no known cognitive or musculoskeletal conditions (N = 26, 6 F; aged 20.85 ± 3.31 years) completed a randomised, counterbalanced, within-subject crossover study involving three warm-up conditions: control (CON), breathing regulation (BR), and breathing regulation plus oculomotor priming (BROC). All conditions included the control warm-up (2-min jog, 10 squats, and 10 walking lunges). BR added 2 min of guided 4:6 breathing, and BROC added 2 min of guided 4:6 breathing plus five oculomotor exercises lasting approximately 2.5 min. Ten familiarisation trials preceded testing at each session. Median visual search time was the primary outcome, while accuracy was analysed to examine potential speed-accuracy trade-offs. Friedman tests evaluated overall condition effects, followed by planned Wilcoxon signed-rank comparisons. Median search times were 2189.70 ms (95% bootstrap CI: 1967.80-2275.90) in CON, 2124.40 ms (95% bootstrap CI: 2027.30-2260.90) in BR, and 1967.60 ms (95% bootstrap CI: 1858.00-2146.20) in BROC. The overall effect of condition was not significant. Participants identified targets faster after BROC than after the control condition (W=89, P<0.05). No differences were seen between CON and BR (P=n.s.) or BR and BROC (P=n.s.). Accuracy was similar across conditions ($\chi^2(2)=1.27$, P=n.s.), suggesting that

participants were not simply trading accuracy for speed. The integrated breathing and oculomotor warm-up was associated with faster target identification relative to control, improving target identification by approximately 222 ms without reducing accuracy. Breathing regulation alone did not improve search performance. Although the omnibus condition effect was not significant, the planned comparison supports BROC as the most promising acute warm-up strategy for improving perceptual-attentional speed in trained collegiate athletes.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.01/CC25

Topic: F.03. Basal Ganglia

Support: American Parkinson Disease Association (APDA) 1053521
UM Frankel Innovation Initiative
Udall Parkinson's Foundation Research Center of Excellence

Title: Aperiodic spectral features of the human subthalamic nucleus across wakefulness and general anesthesia in Parkinson's Disease

Authors: *M. BAUMHAUER[1], I. HAINDL[1], K. CHEN[2], D. K. LEVENTHAL[3], E. OPRI[4]; [2]Neurosurg., [3]Neurol., [4]BME, [1]Univ. of Michigan, Ann Arbor, MI

Abstract: The subthalamic nucleus (STN) is a key deep brain stimulation target in Parkinson's disease (PD), and local field potentials (LFPs) recorded from this region provide insight into disease and neural state dynamics. While oscillatory activity has been extensively studied, less is known about the aperiodic component of the power spectrum, particularly across wakefulness and general anesthesia (GA). We recorded STN LFPs from 12 patients with PD during awake and GA states. Aperiodic spectral features were quantified using both irregular resampling auto-spectral analysis (IRASA) and fitting oscillations and one-over-f (FoooF/spectparam). IRASA was computed on a frequency range of 8-350hz to characterize broad spectrum changes while FoooF was computed from 8-100hz to avoid spectral knee effects. We compared IRASA-derived mean aperiodic power and FOOOF-derived aperiodic exponent across behavioral states and electrode contacts located inside versus outside the STN, determined by MNI based lead reconstruction from pre and postoperative imaging. Spatial distributions were visualized in MNI space. Statistical comparisons used paired t-tests. Across subjects, mean aperiodic power was greater during wake than GA both inside ($p<0.001$) and outside ($p<0.001$) the STN, with a significantly larger wake-GA difference inside the STN ($p<0.001$). MNI mapping localized this effect to the STN region. The exponent was greater during GA than wake both inside ($p <0.001$) and outside ($p<0.001$) the STN, but the GA-wake difference did not differ by contact location

(p=0.7). During wakefulness, mean aperiodic power and the aperiodic exponent were significantly correlated ($p < 0.001$, $R^2 = 0.36$), but this relationship was absent during GA ($p = 0.4$, $R^2 = 0.007$). These findings show how aperiodic spectral features of STN LFPs differ across location and state (wakefulness and GA) in patients with PD. Wakefulness is associated with increased mean aperiodic power, particularly within the STN, whereas GA is associated with a steeper aperiodic exponent across regions. The loss of correlation between aperiodic power and exponent during GA suggests that these features capture distinct aspects of neural state and provide complementary information beyond traditional oscillatory analyses.

Disclosures: M. Baumhauer: None. **I. Haindl:** None. **K. Chen:** None. **D.K. Leventhal:** None. **E. Opri:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.02/CC26

Topic: F.03. Basal Ganglia

Support: USF research grants
University of South Dakota

Title: Altered Subthalamic Nucleus Firing Dynamics in people with Parkinson's Disease and Freezing of Gait During Lower-Limb Motor Tasks

Authors: *V. BHARMAURIA[1], K. HOANG[1], Y. B. BEZCHLIBNYK[1], O. FLOUTY[1], A. SINGH[2];
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Abstract: Freezing of gait (FOG) is a debilitating symptom of Parkinson's disease (PD) associated with dysfunction of basal ganglia locomotor circuits. While abnormal subthalamic nucleus (STN) activity has been implicated in motor impairment, differences in STN neuronal firing and firing dynamics between PD with FOG (PDFOG+) and PD without FOG (PDFOG-) during lower-limb motor tasks remain incompletely understood. To address this question, we performed intraoperative microelectrode recordings (MER) from the STN during deep brain stimulation surgery in PD patients while they completed a cycling paradigm consisting of rest, pedaling (Ped), and dual-task pedaling (Ped+Cog; serial subtraction during pedaling). STN spikes were sorted and tracked across behavioral conditions, and patients were classified as PDFOG+ or PDFOG- based on NFOGQ assessment. PDFOG+ (n = 79 neurons) exhibited consistently higher STN firing rates than PDFOG- (n = 78 neurons) across all task conditions. At rest, mean firing rates were 24.6 ± 2.8 Hz in PDFOG+ and 17.0 ± 1.8 Hz in PDFOG- ($p = 0.151$). During lower-limb motor task (pedaling), firing rates decreased substantially in PDFOG- (9.5 ± 1.3 Hz) but remained elevated in PDFOG+ (21.2 ± 3.2 Hz), resulting in a trend toward a group difference ($p = 0.090$). During the dual-task (Ped+Cog) condition, firing rates remained

higher in PDFOG+ (23.0 ± 3.5 Hz) than in PDFOG- (8.6 ± 1.4 Hz). In addition to reduced firing rates, PDFOG- exhibited significantly lower log(ISI) peak values, defined as the peak location of a Gaussian fit to the log-transformed inter-spike interval distribution ($p = 0.0057$), coefficient of variation (CV; $p = 0.0081$), local variation (LV; $p = 0.0039$), and burst index (BI; $p = 0.0016$) during lower-limb motor task. Similar differences were observed during dual-task for log(ISI) peak values ($p = 0.0021$), CV ($p = 0.0009$), and BI ($p = 0.0010$), whereas LV was not significantly different ($p = 0.6355$). Together, these findings demonstrate that PDFOG+ exhibit persistently elevated STN firing rates and greater firing irregularity during mower-limb movements. In contrast, PDFOG- show marked task-related suppression of STN activity accompanied by increased firing sparseness, reduced firing variability, and less burst-prone activity. These results suggest that impaired regulation of STN neuronal activity may contribute to the pathophysiology of FOG in PD and highlight distinct neuronal signatures associated with lower-limb motor dysfunction.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR317.03/CC27

Topic: F.03. Basal Ganglia

Support: NIH Grant 1R24MH140088

Title: Task-Derived GPi-Motor Cortical Synchrony States Link Behavioral Burden and DBS Physiology in Parkinson's Disease

Authors: *S. YOOK[1], N. POURATIAN[2], J. CHOI[3], A. ALIJANPOUROTAGHSARA[4], H. KIM[5], A. W. TOGA[6];
[1]Neuroimaging and Informatics Institue, Univ. of Southern California, Los Angeles, CA; [2]Southwestern Med. Ctr., Dallas, TX; [3]Neurolog. Surgery, Univ. of Texas Southwestern Med. Ctr., Corinth, TX; [4]Univ. of Texas, Southwestern Med. Ctr., Dallas, TX; [5]Stevens Neuroimaging and Informatics Inst., Los Angeles, CA; [6]USC Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA

Abstract: Deep brain stimulation (DBS) improves symptoms of Parkinson's disease, but it remains unclear how stimulation changes patients' states within task-relevant circuit states. Biomarkers are measured at rest or as isolated features, whereas impairment emerges as patients transition into preparation, conflict, and action. We tested whether globus pallidus internus (GPi)-motor cortical synchrony defines a task-derived state space for interpreting motor burden and DBS physiology.Data comprised 39 GPi-motor cortical recordings, accessed through the Data Archive for the BRAIN Initiative (DABI). Behavioral data included two contexts: motor

release, contrasting externally cued movement (37 subjects/644 windows) with self-initiated movement (11/336), and flanker conflict, contrasting congruent and incongruent trials (4/981). DBS included rest blocks (6/81). GPi and motor-strip ECoG contacts were averaged regionally. Low-beta (13-20 Hz) features quantified coupling, timing, co-bursting, and phase slips. Subject-centered PCA mapped task windows into latent space; DBS rest was projected into the same coordinates.The space yielded two dimensions: PC1 was associated with low-beta co-bursting and PC2 with GPi-cortical timing. During motor release, self-initiated movement separated from externally cued movement along the low-beta co-bursting side at phase 2 pre-final preparation ($p=0.008$). During flanker conflict, incongruent trials showed greater trajectory burden than congruent trials ($p=0.002$). These burden directions were closely aligned across tasks (cosine=0.9997). DBS rest occupied patient-specific positions; in paired subjects, it shifted from phase 1 start toward phase 2 self-preparation in 5 of 6 subjects.These findings suggest three points. First, burden may peak during pre-final preparation, before immediate pre-movement and execution. Second, motor-release and conflict-control demands may converge on a common pre-action synchrony geometry, without implying the same mechanism. Third, DBS may reposition the motor starting state toward preparation, reducing the transition needed for self-initiation rather than accelerating execution. Together, these results support a patient-level latent-space framework for interpreting DBS physiology.

Disclosures: S. Yook: None. **N. Pouratian:** Other; Abbott, Boston Scientific, Medtronic, BrainLab. **J. Choi:** None. **A. Alijanpourotaghsara:** None. **H. Kim:** None. **A.W. Toga:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.04/CC28

Topic: F.03. Basal Ganglia

Support: NINDS UH3NS103468
NINDS UH3NS129898

Title: Real-time control of basal ganglia phase-locking demonstrates causal role of information transmission in Parkinsonian bradykinesia.

Authors: *S. L. SCHMIDT[1], R. RODRIGUEZ CAPILLA[3], J. PETERS[2], H.-J. LEE[2], D. A. TURNER[3], W. M. GRILL[2];
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Abstract: Deep brain stimulation (DBS) is an effective therapy for the motor symptoms of Parkinson's disease (PD), but the therapeutic mechanisms remain incompletely understood. Computational and preclinical studies suggest that DBS may create an information lesion by disrupting communication (both pathological and physiological) in the stimulated nucleus.

However, this mechanism has not been tested in persons with Parkinson's receiving therapeutic DBS. Here we tested whether adaptive DBS regulating the level of information flow between the subthalamic nucleus (STN) and globus pallidus (GP) could control the severity of bradykinesia in PD. All study activities were approved by the FDA and Duke University Health System IRB, and all participants provided informed consent. We recorded chronic local field potentials from bilateral STN and GP electrodes in participants with a Summit RC+S implantable pulse generator (donated by Medtronic, Inc.) during monthly research visits. We quantified beta band phase locking value (PLV) as a measure of interregional information transmission. In the absence of DBS, intrahemispheric (STN - GP) PLV was significant in 562 of 572 observations and was higher than interhemispheric PLV between contralateral STNs or GPs (mean difference and CI: 0.104 [0.090, 0.118] and 0.134 [0.120, 0.148], respectively; $p < 10^{-3}$). In experiments with randomized 10-second DBS amplitudes, PLV decreased with increasing DBS amplitude in at least one hemisphere in all participants. These findings suggest that interregional beta synchronization is consistently present and that DBS is associated with a graded informational lesion. We then tested whether manipulating PLV causally altered motor behavior. In five participants, DBS amplitude was adapted in real time to maintain specified PLV setpoints during 300-second experiments (i.e., PLV guided adaptive DBS). In this framework, the controller targeted the level of the interregional synchronization rather than directly adjusting the DBS amplitude or motor output. Increasing the PLV setpoint by 0.1 reduced the mean DBS amplitude by 18.22% (CI: [20.61%, 15.83%], $p < 10^{-3}$), allowing greater intrahemispheric synchronization. Increasing the PLV setpoint also slowed hand grasp movements (mean and CI: -0.534 [-0.698, -0.371] Hz, $p < 10^{-3}$), indicating worsening bradykinesia. These findings provide experimental evidence supporting a causal link between DBS-induced suppression of interregional beta synchronization and improvement in bradykinesia in people with PD.

Disclosures: S.L. Schmidt: None. **R. Rodriguez Capilla:** None. **J. Peters:** None. **H. Lee:** None. **D.A. Turner:** None. **W.M. Grill:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.05/CC29

Topic: F.03. Basal Ganglia

Support: NIH/NINDS (R01 NS125143)
NIH/NINDS (K23 NS097576)

Title: Activation of neural pathways in the subthalamic region depends on stimulation polarity

Authors: *S. BORGHEAI[1], E. OPRI[3], F. ISBAINE[4], N. G. LAXPATI[5], B. RISK[1], J. WILLIE[6], R. E. GROSS[7], N. AU YONG[1], C. MCINTYRE[8], S. MIOCINOVIC[2];
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Abstract: There is limited understanding regarding which subcortical pathways are activated by deep brain stimulation (DBS). Our goal is to elucidate biophysical mechanisms of subthalamic pathway recruitment by studying stimulus polarity (cathodic vs. anodic), inspired by clinical observations that the DBS therapeutic response is polarity-dependent. We measured electrophysiologic activation of three clinically-relevant subthalamic pathways- the cortico-subthalamic hyperdirect pathway (HDP), subthalamopallidal pathway (STN-GP), and cortico-spinal/bulbar tract (CSBT)- in 15 patients with Parkinson's disease undergoing awake DBS surgery. Cortical evoked potentials (cEP) were recorded using temporary subdural electrocorticography (ECoG). DBS local evoked potentials (DLEP) were recorded from non-stimulating contacts and muscle activity (via electromyography [EMG]) was recorded from upper limb and facial muscles. We quantified: a) the amplitude of short-latency cEP, previously shown to mirror activation of the cortico-STN hyperdirect pathway, b) DLEP amplitude, believed to be attributed to the activation of STN-globus pallidus (GP) pathway, and c) amplitudes of very short-latency cEP and motor evoked potentials (mEP) for activation of cortico-spinal/bulbar tract (CSBT). We constructed recruitment and strength-duration curves for each EP and pathway to compare the excitability in response to different stimulation polarities. Next, we compared experimental data with the most advanced DBS computational models. Our results provide experimental evidence that relative efficiency for pathway activation varies by polarity such that anodic stimulation is the least efficient in activating CSBT, moderately efficient for HDP, and as efficient as cathodic in activating the STN-GP pathway. Additionally, we demonstrate that subcortical cathodic and anodic stimulation activate the same pathways in the STN region and that cathodic stimulation is in general more efficient. We further discuss how DBS computational modeling and fundamental biophysical principles predict distinct effects of stimulus polarity on passing axons, axon terminals, and local neuronal elements. Finally, we relate our findings to prior clinical DBS studies, providing additional evidence that activation of the hyperdirect pathway may contribute to the therapeutic mechanisms underlying DBS.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.06/CC30

Topic: F.03. Basal Ganglia

Title: Spectral Characterization of Single-Neuron Spiking in the Human Subthalamic Nucleus

Authors: *Y. SALIMPOUR[1], T. ARGINTEANU[3], K. WYSE-SOOKOO[4], K. A. MILLS[2], W. S. ANDERSON[5];
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Abstract: Pathological synchronization in the beta frequency band within the motor network is a hallmark of Parkinson's disease (PD) and is considered a biomarker for assessing disease state and for closed-loop deep brain stimulation (DBS). While beta-band activity is well characterized in local field potentials (LFPs) and using spectral analysis, the spectral structure of spiking activity from individual subthalamic nucleus (STN) neurons is less understood, in part because spectral estimation of spike trains poses challenges distinct from those of continuous signals. This limits the clinical and translational applications of single-cell recordings from the STN. To address this gap, we apply a dedicated point-process spectral analysis method using an FFT-based procedure to quantify the frequency content of single-neuron spiking in the human STN. We recorded single neuron spiking activities from the STN of patients with PD undergoing awake DBS lead placement surgery. Target verification and identification of single neuron recordings were verified by the neurologist intraoperatively. Spike timing of single neurons was identified via offline spike sorting, and the spectrum of each spike train was estimated using a point-process spectral estimator. Each recording was divided into discrete segments, tapered with a sliding window, and the resulting periodograms were averaged to obtain the unit power spectrum. Statistical significance was determined using surrogate spike trains generated by randomly shuffling the original interspike intervals. Across the recorded population of neurons from STN, we identified individual neurons with elevated power in the beta band relative to neighboring frequencies, indicating that beta-rhythmic structure is expressed at the level of individual STN Neurons and is not limited to LFPs. These findings demonstrate that pathological features associated with Parkinsonian state, such as exaggerated neuronal oscillations recoverable from single-cell spiking activity, and the spectral analysis provides a principled framework for extracting them. In conclusion, this single-unit approach may complement LFP-based measures for monitoring disease state and offers a Parkinson’s disease biomarker in a single cell resolution for closed-loop DBS systems.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.07/DD1

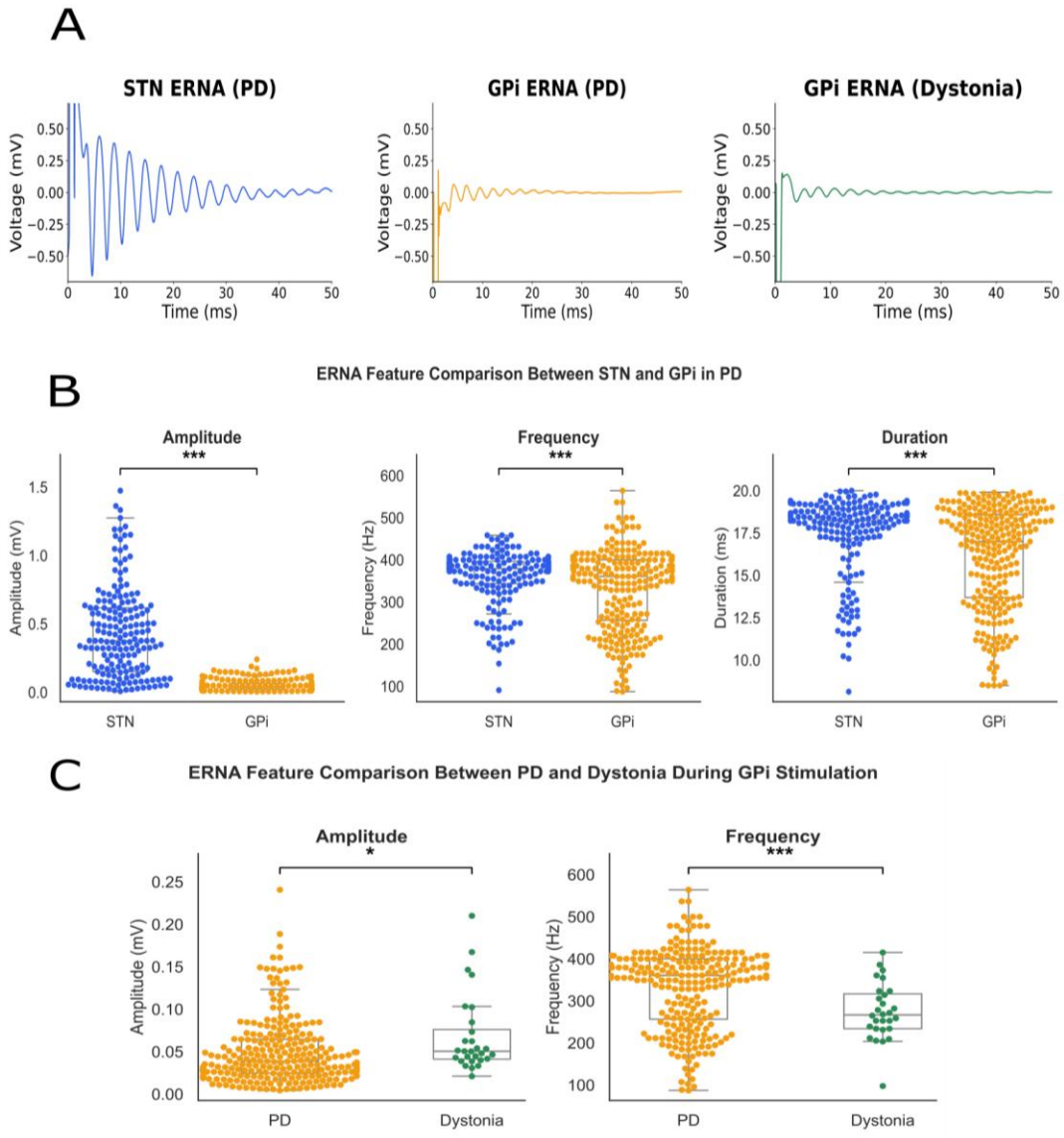
Topic: F.03. Basal Ganglia

Support: R00NS137249
Parkinson's Foundation

Title: Evoked Resonant Neural Activity During Deep Brain Stimulation Reflects Target and Disease Specific Physiology in Parkinson's Disease and Dystonia

Authors: *E. VEGA[1], P. COUTINHO[2], F. PEREIRA SARMENTO[3], J. WONG[2], J. HILLIARD[2], K. FOOTE[2], C. DE HEMPTINNE[2], K. A. JOHNSON[1];
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Abstract: Evoked resonant neural activity (ERNA) is a stimulation-evoked potential that shows promise as a biomarker to guide deep brain stimulation (DBS) therapy. Although ERNA has been observed during subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS in both Parkinson's disease (PD) and dystonia, target and disease-specific differences remain unclear. The objective of this study was to compare ERNA features across targets and across PD and dystonia to identify target- and disorder-specific physiological signatures. Intraoperative local field potentials during bursts of high-frequency stimulation to elicit ERNA were recorded during DBS implantation in 95 patients with PD (108 hemispheres; 37 STN, 71 GPi; age 66.6 ± 7.6 years, 25 females, 70 males) and 7 patients with dystonia (8 hemispheres; 8 GPi; age 54.0 ± 18.5 years, 5 females, 2 males). ERNA peaks were identified using automated peak detection and defined from the first peak to the final trough. Feature extraction was performed at each contact, including amplitude, frequency, latency, duration, and exponential rise/decay time constants. Group differences were assessed using Welch's two-sample t-tests. In PD, STN ERNA was higher amplitude ($p<0.001$), higher frequency ($p=0.0012$), and longer duration ($p<0.001$) than GPi; latency and rise/decay constants did not differ. During GPi stimulation, dystonia showed greater ERNA amplitude ($p=0.0429$) and lower frequency ($p=0.0002$) than PD, while all other features were similar between groups. ERNA features differed across stimulation targets and diagnoses, supporting ERNA as a marker of target and disease-specific basal ganglia physiology to guide individualized DBS targeting and programming. Future studies will evaluate whether ERNA-based machine learning models can predict optimal contact selection and long-term DBS outcomes.



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Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR317.09/DD2

Topic: F.03. Basal Ganglia

Support: USF Research Grant

Title: Comparative Analysis of Neuronal Waveforms and Firing Patterns in the Human STN and Gpi

Authors: *J. VANDERPOOL[1], K. HOANG[1], J. SINGH[1], S. MOLOTCHNIKOFF[2], O. FLOUTY[1], Y. B. BEZCHLIBNYK[1], V. BHARMAURIA[1];
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Abstract: Subthalamic nucleus (STN) and Globus pallidus internus (GPi) are major deep brain stimulation (DBS) targets for Parkison's disease (PD). The STN predominantly contains glutamatergic neurons providing excitatory drive to basal ganglia structures, including the GPi. The GPi is the principal output nucleus, containing GABAergic neurons that inhibit the thalamus. Although microelectrode recordings (MER) acquired during DBS surgery often reveal characteristic waveform and firing patterns that may reflect local cellular and network organization, systematic comparisons of neuronal waveform morphology and firing properties between the STN and GPi remain limited. We characterized MER spike waveforms from the STN [n = 11 patients (17 hemispheres); N = 700 neurons] and GPi [n = 15 patients (27 hemispheres); N = 561 neurons] during DBS surgery in PD patients. Using peak-to-trough time (spike-width) on normalized waveforms, spikes were classified into three classes: triphasic (peak preceding trough), fast-spiking (FS, <250 μs), and regular-spiking (RS, ≥250 μs). Firing rate and ISI-derived metrics were computed from ISI histograms (0.5 ms bins), including coefficient of variation (CV), short-ISI proportion (<10 ms), burst index (BI), and pause probability (>50 ms). Group differences were assessed with Kruskal-Wallis and pairwise Mann-Whitney U tests; effect sizes reported as η^2 and rank-biserial r. In the GPi, 136 triphasic, 157 FS, and 268 RS neurons were characterized. Firing rate, pause probability, and remaining ISI metrics showed no significant differences across triphasic and RS comparisons. FS units showed greater CV than both RS ($U = 14{,}822$, $p = 0.003$, $r = 0.181$) and triphasic units ($U = 10{,}242$, $p = 0.021$, $r = 0.165$; KW $p = 0.008$, $\eta^2 = 0.019$). Short-ISI proportion was likewise greater in FS versus RS ($U = 14{,}979$, $p = 0.004$, $r = 0.172$) and triphasic units ($U = 10{,}116$, $p = 0.034$, $r = 0.150$; KW $p = 0.013$, $\eta^2 = 0.017$). FS units also showed greater BI versus RS ($U = 14{,}980$, $p = 0.004$, $r = 0.172$) and triphasic units ($U = 10{,}120$, $p = 0.034$, $r = 0.151$; KW $p = 0.013$, $\eta^2 = 0.017$). In the STN, 145 triphasic, 200 FS, and 355 RS neurons were characterized. No significant differences were observed across waveform classes for any firing metric (all KW $p \geq 0.54$, all pairwise $p \geq 0.29$, all $r \leq 0.054$). In conclusion, FS GPi neurons demonstrate greater firing irregularity, short-ISI proportion, and BI compared with RS and triphasic neurons, indicating functional distinction in temporal firing dynamics. These differences may reflect distinct cellular and network organization within the GPi and STN, with implications for MER-based cell type classification during DBS surgery.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR317.10/DD3

Topic: F.03. Basal Ganglia

Support: Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada (RGPIN-2020-05868)

Title: Frequency-dependent Inhibition during Deep Brain Stimulation of Thalamic Ventral Intermediate Nuclei as a Physiological Correlate for Essential Tremor

Authors: *M. LANKARANY, **Z. PARASKEVOPOULOS**;
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Abstract: Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (Vim) has been a standard therapy for essential tremor. It has been shown that high frequency (≥100Hz) DBS suppresses Vim firing and tremor activity. Here, we investigate whether neuronal suppression during high-frequency DBS occurs at cellular levels or is influenced by network-level effects. Using human in vivo recordings of Vim neurons during different DBS frequencies, we detected a positive-going evoked-field potential during high-frequency Vim-DBS in some recording sites. Interestingly, it was observed that (i) neuronal suppression is stronger in neurons with the evoked potential, implying that inhibitory engagement during high-frequency DBS can further suppress neuronal firing, (ii) the evoked potential emerges after the transient burst, i.e., the latter may give rise to the former, and (iii) applying microstimulation to neurons with the evoked potential results in increased tremor reduction. We showed that the occurrence of inhibitory activity is negatively correlated with firing, and neurons with the evoked potential are significantly more suppressed than those without. Moreover, we verified that stimulation sites with the evoked potential are significantly correlated with increased accelerometer tremor reduction. We propose a framework that explains DBS effects at both cellular and network levels, i.e., high-frequency DBS not only depresses synapses, but also enables the recruitment of inhibitory neurons. A transient burst in the spiking activity is likely providing sufficient network engagement to recruit inhibitory neurons that are silent during low-frequency DBS. For the first time, we analyzed 300 Hz microstimulation and found only one sample with evoked potentials, and that 300 Hz stimulation does not induce an initial excitatory firing burst, further supporting our hypothesized mechanism of inhibition recruitment. Additionally, the percent of stimulation pulses associated with an evoked potential is positively and significantly correlated with accelerometer tremor reduction. Lastly, we found that the distance from the recording site to the Vim-ventral caudal border is anti-correlated with the percent of stimulation pulses associated with evoked potentials. This aligns with previous literature highlighting that with increased proximity to the ventral caudal border, a higher percent tremor reduction is observed.

Disclosures: M. Lankarany: None. **Z. Paraskevopoulos:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.11/DD4

Topic: F.03. Basal Ganglia

Support: Raynor Cerebellum Project

Title: Multichannel artifact suppression reveals sub millisecond evoked potentials and spiking activity during deep brain stimulation

Authors: *S. JAVADZADEH NO[1], R. SOROUSHMOJDEHI[1], A. SEYYED MOUSAVI[1], T. D. SANGER[2,1];
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Abstract: Electrical artifacts during deep brain stimulation (DBS) can exceed neural signals by orders of magnitude, obscuring evoked potentials (EPs) and preventing spike analysis during stimulation. This challenge is severe during high-frequency stimulation, where artifacts overlap and conventional template subtraction can remove or distort early neural responses. We developed a multichannel artifact-removal framework for human intracranial microelectrode recordings that exploits the spatial structure of stimulation artifacts across simultaneously recorded channels. Artifact peaks were detected, and channels were selected as predictors based on polarity-insensitive pulse-to-pulse artifact similarity and artifact magnitude. Signed artifact peaks were then used to fit a constrained linear artifact-reference montage for each target channel. This approach does not require a specialized stimulation protocol or averaging across pulses. We extended it by incorporating contralateral channels and short-lagged predictor samples, allowing the model to capture artifact waveform differences caused by filtering, aliasing, and electrode-specific temporal distortions while preserving a stationary transformation of the continuous signal. This approach removed artifacts hundreds of times larger than underlying spikes without requiring local interpolation or deletion of stimulation-locked data. Unlike template subtraction, this method tolerated aliasing and preserved very early EP components occurring approximately 0.4 ms after the stimulation artifact peak, which were otherwise obscured or attenuated. The method also enabled EP tracking during stimulation frequencies up to 1000 Hz. After artifact suppression, we used extracted EPs to construct optional EP-removal templates during stimulation, producing signals suitable for standard spike sorting. Spike sorting of the cleaned recordings revealed two complementary forms of activity under stimulation: stimulus-locked spiking captured by peri-stimulus time histograms, and ongoing background spiking that allowed estimation of firing-rate changes and other spiking characteristics, such as inter-spike interval changes, across stimulation conditions. Temporal changes in background spiking were comparable with EP dynamics, suggesting that stimulation altered both evoked and ongoing neural activity. Together, these results show that multichannel artifact suppression can recover sub millisecond EPs and spiking activity during DBS, enabling simultaneous analysis of evoked responses and single-unit activity under stimulation conditions that were previously inaccessible.

Disclosures: S. Javadzadeh No: None. **R. Soroushmojdehi:** None. **A. Seyyed Mousavi:** None. **T.D. Sanger:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.12/DD5

Topic: F.03. Basal Ganglia

Title: Stimulation-evoked potentials reveal differential basal ganglia circuit engagement during deep brain stimulation

Authors: *S. SUMARAC;
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Abstract: Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is therapeutic in both Parkinson's disease (PD) and dystonia, yet these disorders are characterized by distinct basal ganglia dysfunction. PD is associated with underactive direct-pathway and overactive indirect-pathway output, whereas dystonia is thought to involve maladaptive plasticity and overactivity of both pathways. Since the GPi receives convergent input from multiple basal ganglia pathways, therapeutic benefit may depend on which pathways are engaged by stimulation, and the optimal pathway to recruit may therefore differ between PD and dystonia. To probe this, we used intraoperative microelectrode recordings during DBS surgery to read out pathway-specific recruitment from two stimulation-evoked responses. Striatal-mediated field evoked potentials (fEPs) in GPi provide a physiological readout of direct-pathway recruitment, whereas evoked resonant neural activity (ERNA) reflects recurrent activity within the STN-GPe network. In PD, brief high-frequency stimulation produced long-term potentiation (LTP)-like enhancement of GPi fEPs alongside rapid short-term depression. In dystonia, the same protocol produced weaker potentiation and slower-adapting depression. ERNA also differed across disorders despite the shared target, showing a higher recurrent peak ratio in dystonia driven by a reduced or absent second peak. Differences in fEP plasticity and ERNA morphology suggest that the same GPi stimulation protocol engages distinct combinations of direct-pathway and STN-GPe network activity in PD and dystonia. In PD, rapid depression coupled with LTP-like enhancement of direct-pathway responses suggests that these inputs are weakened yet remain capable of potentiation, whereas robust ERNA indicates recruitment of recurrent STN-GPe dynamics. Therapeutic benefit may therefore arise from preferential engagement of recurrent STN-GPe dynamics reflected by ERNA, together with stimulation paradigms that preserve or enhance direct-pathway efficacy rather than further depressing already underactive inputs. In dystonia, where both direct- and indirect-pathway activity are thought to be excessive, weaker potentiation and more persistent depression of direct-pathway responses suggest that therapeutic benefit may instead arise through progressive suppression of pathological direct-pathway activity, alongside modulation of recurrent STN-GPe dynamics. These results suggest that GPi

DBS does not act through identical circuit mechanisms across movement disorders and that evoked responses may provide biomarkers of pathway engagement relevant to therapy.

Disclosures: S. Sumarac: None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.13/DD6

Topic: F.03. Basal Ganglia

Support: Raynor Cerebellum Project

Title: Ultra high frequency deep brain stimulation induces activity dependent modulation of neural excitability in humans

Authors: *R. SOROUSHMOJDEHI[1], A. SEYYED MOUSAVI[1], S. JAVADZADEH NO[1], T. D. SANGER[2,1];
[1]Univ. of California Irvine, Irvine, CA; [2]Res., Children's Hosp. of Orange County, Orange, CA

Abstract: Deep brain stimulation (DBS) can reshape circuit activity across multiple timescales, yet the mechanisms linking stimulation frequency to neural excitability remain poorly understood. Ultra high frequency stimulation (UHFS; ~1 kHz) is increasingly relevant for neuromodulation and is often interpreted as suppressing neural activity. However, whether UHFS produces inhibition or structured, activity dependent modulation of circuit responsiveness remains unclear. Here, we used UHFS as a mechanistic perturbation to examine how kilohertz stimulation alters DBS evoked potentials (EPs) in human basal ganglia thalamic circuits.We analyzed stimulation EPs recorded from basal ganglia and thalamic structures in pediatric dystonia patients undergoing DBS. EPs were measured during conventional frequency probe blocks interleaved with UHFS epochs. Because individual responses during UHFS could not be reliably isolated from stimulation artifact, changes in probe EP amplitude were used as a readout of UHFS induced changes in circuit excitability.Across subjects and contacts, UHFS produced progressive modulation of EP amplitudes across repeated stimulation cycles. This modulation was bidirectional: some contacts showed facilitation, whereas others showed depression or mixed responses. Despite heterogeneity in direction, responses shared a common temporal structure characterized by gradual accumulation, saturation with repeated exposure, persistence after UHFS, and partial or complete recovery after stimulation cessation.To interpret these dynamics, we used a physiologically constrained computational model. The model captured key temporal features of the data, including bidirectional modulation, saturation, persistence, and recovery, while allowing modulation direction and magnitude to vary across contacts and regions. Model based analysis suggested that UHFS effects evolve over timescales longer than individual pulses or blocks, indicating that kilohertz stimulation alters neural responsiveness through slowly evolving physiological state changes rather than all or none silencing.These

findings suggest that UHFS does not simply suppress human neural circuits but induces structured, activity dependent modulation of DBS evoked responses. Facilitation and depression indicate that modulation direction depends on local circuit physiology, while shared temporal dynamics suggest a conserved stimulation driven process. By linking stimulation frequency, EPs, and evolving circuit excitability, this work provides a framework for studying DBS induced plasticity like mechanisms across seconds to minutes timescales.

Disclosures: R. Soroushmojdehi: None. **A. Seyyed Mousavi:** None. **S. Javadzadeh No:** None. **T.D. Sanger:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

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Program #/Poster #: PSTR317.14/DD7

Topic: F.03. Basal Ganglia

Support: NIH (NINDS) T32 NS115724
American Parkinson Disease Association (APDA) 1053521
UM Frankel Innovation Initiative
Udall Parkinson's Foundation Research Center of Excellence

Title: Context-Dependent Morphology of DBS Local Evoked Potentials Across Movement and Anesthesia

Authors: *E. BENCE[1], E. GADZIC[5], P. S. LAKSHMANAN[2], R. WANG[1], E. URIBE[1], R. ABEDINPOUR[1], A. HESTON[3], K. CHOU[3], E. L. LEVIN[4], K. CHEN[4], D. K. LEVENTHAL[3], E. OPRI[2];
[2]BME, [3]Neurol., [4]Neurosurg., [1]Univ. of Michigan, Ann Arbor, MI; [5]Johns Hopkins Univ., Baltimore, MD

Abstract: This study investigates how behavioral and anesthetic states modulate deep brain stimulation local evoked potentials (DLEPs) in Parkinson's Disease (PD). Local field potentials were recorded from 16 patients undergoing subthalamic nucleus deep brain stimulation implantation. In a subset of 4 awake patients, recordings were obtained at rest and during a cued contralateral hand-movement task. In 12 additional patients, bilateral recordings were obtained at rest during both wakefulness and general anesthesia. To quantify state-dependent changes in DLEP morphology, we independently characterize amplitude and frequency changes using a self-referenced template-matching stretch/compression factor with lag correction to ensure precise signal alignment, for each contact, independently.
Movement behavior modulated DLEP morphology within patients. During contralateral hand movement, DLEP amplitude decreased in three of four patients compared with rest ($p < 0.05$), while DLEP frequency changes were partially heterogeneous, as it was significantly lower in two patients and higher in one ($p < 0.05$). General anesthesia consistently and significantly reduced

DLEP amplitude across patients. Relative to awake recordings, median DLEP amplitude under general anesthesia decreased by 60.9% during 130 Hz burst stimulation ($p < 0.01$) and by 63.7% during 11 Hz stimulation ($p < 0.01$). DLEP frequency also decreased significantly under general anesthesia, with a median change of 11.8% at 130 Hz stimulation ($p < 0.01$), whereas no significant temporal change was observed at 11 Hz stimulation.
These findings demonstrate that DLEPs exhibit complex, context-dependent morphology across behavioral and anesthetic states. Characterizing state-dependent modulation of evoked responses during movement and altered consciousness may be critical for designing robust DLEP-based intraoperative mapping and closed-loop DBS systems capable of adapting to real-world neural and behavioral variability.

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Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

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Topic: F.03. Basal Ganglia

Support: Vibrotactile Therapy Research Fund (PTA: GHIQI)
Michael and Elizabeth Ogie Research Fund (GHKRD)
Ogie Family Fund (GHJCD)
Alan and Arlene Alda Parkinson's Research Fund (GHILL), Stanford University

Title: Vibrotactile coordinated reset for acute and long-lasting motor improvement and neural engagement in Parkinson's disease

Authors: *S. ZHOU[1], K. CHAUHAN[1], S. KUMAR[3], J. M. HENDERSON[1], V. BUCH[1], W. MARKS[2], P. A. TASS[1];
[1]Neurosurg., [2]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA; [3]Stanford Hlth. Care, Stanford, CA

Abstract: Parkinson's disease (PD) is characterized by pathological neural synchrony in sensorimotor networks. Vibrotactile Coordinated Reset (vCR) is a non-invasive neuromodulation therapy delivering patterned vibrotactile stimulation via a wearable glove to induce neural desynchronization through plasticity mechanisms. However, prior-generation vCR showed substantial inter-individual variability in motor improvement, particularly in treatment-resistant axial symptoms, partly due to suboptimal stimulation that insufficiently recruited peripheral mechanoreceptors, limiting thalamocortical neural engagement. To address this, we developed a next-generation vCR glove with optimized stimulation to enhance peripheral somatosensory recruitment and sensorimotor neural engagement. Twelve PD patients received daily home-based

next-generation vCR (two 2-hour sessions/day), with off-medication MDS-UPDRS III assessments at Day 1 and at 3 and 6 months. Simultaneous 64-channel electroencephalography (EEG) was recorded during a 15-min vCR session (5-min resting-state pre/post-stimulation), and a dynamic neural engagement index (DNEI) was constructed from stimulation-locked EEG features across time, frequency, and spatial domains. Clinical outcomes and DNEI were compared against a prior-generation vCR cohort. Next-generation vCR produced significant off-medication MDS-UPDRS III reductions acutely (Day 1) and cumulatively at 3 and 6 months, with large effect sizes ($|EF|>0.7$, Wilcoxon, $p<0.05$), notably including axial symptoms often refractory to pharmacotherapy and worsened by deep brain stimulation (DBS). Next-generation vCR also significantly enhanced DNEI, with widespread sensorimotor cortical activation (cluster-based permutation, $p<0.05$) and suppression of pathological corticostriatal coupling. Greater DNEI correlated significantly with acute motor improvement in bradykinesia and axial domains (Spearman, $p<0.05$). Cohort comparisons confirmed superior long-term motor outcomes and neural engagement over prior-generation vCR. These findings **represent a significant advance** for effective non-invasive neuromodulation in PD, establishing next-generation vCR as a clinically and neurophysiologically validated approach for treatment-resistant PD motor symptoms.

Disclosures: S. Zhou: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor of Stanford-owned provisional patent application 64/088,342. **K. Chauhan:** None. **S. Kumar:** None. **J.M. Henderson:** None. **V. Buch:** None. **W. Marks:** None. **P.A. Tass:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor of Stanford-owned provisional patent application 64/088,342, and of an additional pending provisional patent application.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.17/DD10

Topic: F.03. Basal Ganglia

Support: 1ZIANS003135-12

Title: Functional mapping of basal ganglia inputs to substantia nigra pars lateralis

Authors: *A. R. PLATT[1], A. BORONAT-GARCÍA[2], L. SANSALONE[3], Z. M. KHALIQ[4]; [1]NINDS/NIH Intramural Res. Program, Bethesda, MD; [2]NINDS/NIH, Bethesda, MD; [3]NINDS, Bethesda, MD; [4]NIH/ NINDS, Bethesda, MD

Abstract: The substantia nigra pars lateralis (SNL) is a dopaminergic subpopulation that is anatomically and functionally distinct from the substantia nigra pars compacta (SNc), yet its circuit-level organization remains poorly characterized. Previous work in our lab has

demonstrated that SNL dopamine neurons receive distinct cortical inputs, suggesting these subpopulations are embedded in divergent circuits. In addition, our past work showed that SNL is involved in aversive behaviors, whereas SNc has been shown to be involved in movement. The SNL receives input from the tail of the striatum, subthalamic nucleus, globus pallidus external segment, and pedunculopontine nucleus. However, how these inputs compare to projections onto canonical SNc dopaminergic neurons, whether they confer distinct synaptic properties, and how they innervate non-dopaminergic neurons in SNL remains unknown. Using a combination of optogenetics, slice electrophysiology, and synaptic tracing, we are currently mapping synaptic inputs to SNL dopaminergic and non-dopaminergic neurons from these regions. Our results show that striatal tail projections to SNL form functional synapses driving direct inhibitory responses in dopaminergic neurons which are mostly mediated by postsynaptic GABAB receptors, and that the SNL has distinct synaptic properties and connectivity patterns across input pathways that distinguish the SNL from the SNc. These findings establish a functional circuit map of inputs to the SNL and reveal that it constitutes a circuit-level distinct nigral subpopulation, laying the groundwork for understanding its specialized contributions to behavior.

Disclosures: A.R. Platt: None. **A. Boronat-García:** None. **L. Sansalone:** None. **Z.M. Khaliq:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR317.18/DD11

Topic: F.03. Basal Ganglia

Support: HHMI Gilliam - GT17029
Michael J Fox Foundation - MJFF-028459
NIH BRAIN Initiative - R00NS112417

Title: Local connectivity defines subpopulations in the pedunculopontine nucleus (PPN)

Authors: *L. RUSS[1], R. C. EVANS[2];
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Abstract: The pedunculopontine nucleus (PPN) is a brainstem region involved in motor control that serves as a therapeutic target for deep brain stimulation (DBS) in Parkinson's Disease (PD) patients. The PPN contains cholinergic, glutamatergic, and GABAergic subtypes and is divided into a rostral and caudal region. Though it is known that the PPN is heavily interconnected with the basal ganglia, we hypothesize that the heterogeneity of the PPN may underlie the highly variable DBS outcomes. Indeed, the rostral and caudal cholinergic PPN have different connectivity with the basal ganglia and may operate as separate populations. However, little is

known about the local circuitry between PPN subpopulations. To determine the degree of local excitatory synaptic input provided to the cholinergic PPN, we injected a CamKIIa-promoted channelrhodopsin (ChR2) into the PPN of ChAT-cre/Ai9 mice and recorded from PPN cholinergic neurons using whole-cell patch clamp electrophysiology and optogenetics to activate CamKIIa-positive PPN cell bodies and axons. We find strong local connectivity from glutamatergic to cholinergic neurons within the PPN, but the strength and characteristics of this synaptic connection did not differ between the rostral and caudal regions. We also see increased intrinsic excitability in cholinergic PPN cells lacking local glutamatergic input. Conversely, we investigate if the cholinergic PPN receives local inhibitory input. We injected a cre-dependent (ChR2) and BiCHATe27-dTomato into Vgat-cre/heterozygous mice and recorded from PPN cholinergic neurons while simultaneously activating Vgat-positive PPN cell bodies and axons. We found that inhibitory PPN neurons innervate both local rostral and caudal cholinergic neurons, but more strongly innervate the caudal region. To understand how local PPN connectivity impacts behavior and calcium activity in an intact circuit, we injected a cre-dependent ChrimsonR and BiCHATe27_GCaMP6f into Vgat-cre and Vglut-cre/heterozygous mice simultaneously activate noncholinergic cell populations while observing neuronal calcium activity in cholinergic PPN cells and general locomotion. Preliminarily, using *in vivo* optogenetics with fiber photometry, we see that optogenetic activation of glutamatergic and GABAergic PPN neurons primarily increases calcium activity in cholinergic PPN cells and decreases general locomotion. Uncovering the local connectivity between PPN subpopulations in a healthy condition at both the circuit and in intact animals will help us better understand how the PPN functions locally to regulate motor function.

Disclosures: L. Russ: None. **R.C. Evans:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

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Topic: F.03. Basal Ganglia

Support: Michael J Fox Foundation - MJFF-028459
NIH BRAIN Initiative - R00NS112417
NIH - T32NS041218

Title: Pedunculopontine nucleus calcium activity is differentially influenced by sensory stimuli

Authors: *M. E. BARTLETT, B. J. BERNSTEIN, P. A. FORCELLI, R. C. EVANS; Georgetown Univ., Washington, DC

Abstract: The pedunculopontine nucleus (PPN) and the superior colliculus (SC) are key brain regions involved in sensorimotor integration. The PPN plays a critical role in locomotor control, and the SC in predator and prey detection. Previous work in the Evans lab has shown these brain

regions are functionally connected. However, there is a gap in knowledge regarding how the connection between these brain regions integrates stimulus detection and action. We hypothesize the connections from the SC to the PPN modulate sensorimotor integration. Understanding the connections between regions is complicated by the heterogeneity of subpopulations within the PPN (cholinergic, glutamatergic, and GABAergic). The SC processes visual information, including light stimulation, looming threats, and visual tracking of prey movement. To determine which, if any, PPN subpopulations are involved in these processes, we ran a battery of visual stimuli, including lights on and off, looming, and the virtual cricket paradigm while recording from each PPN neural subtype utilizing in vivo fiber photometry. We find that all PPN cell types increased activity during light-on stimuli, while none changed in response to prey detection. Interestingly, only the PPN glutamatergic population increased in response to the looming threat, suggesting that visual threat stimuli activate PPN glutamatergic neurons in addition to simple visual stimuli. Taken together, PPN subpopulations display distinct responses to SC axon activation and visual stimuli.

Disclosures: M.E. Bartlett: None. **B.J. Bernstein:** None. **P.A. Forcelli:** None. **R.C. Evans:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.20/DD13

Topic: F.03. Basal Ganglia

Title: Chronic pallidal recordings reveal multi-scale neural dynamics in pediatric dystonia

Authors: *A. BALACHANDAR[1], K. MITHANI[1], T. H. LATYPOV[2], S. COLEMAN[4], C. GORODETSKY[3], G. IBRAHIM[3];
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Abstract: Dystonia is a disabling movement disorder affecting children in which symptoms fluctuate across clinical, developmental and disease states. The neural dynamics that govern these states are poorly understood. We studied local field potentials (LFPs) collected from GPi-DBS electrodes implanted in a diverse cohort of 34 children longitudinally across days-to-years (recording range 1-1603 days), using 1532 time series recordings. We found that pallidal activity was organized around a beta band-synchronized state across multiple scales. Locally, most recordings demonstrated periodic components of the power spectrum within the beta-band (n=863, 19.8±4.5 Hz), consistent in most participants (n=28) independent of age, sex, phenomenology (i.e. tonic vs. phasic) and aetiology (i.e. inherited vs. acquired). This beta-synchronized state was clinically expressed through associations between low-beta LFP power and worse quality-of-life scores (PedsQL, p=0.011), and between beta-band periodic peak power and greater dystonia severity (BFMDRS, p=0.044). At the network level, interhemispheric

imaginary coherence was significantly elevated and greatest in the low-beta band, with low-beta (p=0.032) and peak beta-band (p=0.031) coherence both associated with worse dystonia severity. In contrast, aperiodic broadband power increased with age (p<0.001) but was not associated with clinical severity, suggesting that non-oscillatory activity may index developmental or background pallidal physiology distinct from dystonic clinical states. Across longer timescales, chronic narrowband recordings demonstrated circadian modulation of pallidal beta-band activity, with increased pooled beta-band power around clinical assessments indexing greater dystonia severity (p<0.001) and daytime beta-power concentration associated with worse quality of life (p=0.043). Our findings suggest that pediatric dystonia is characterized by beta band-synchronized pallidal brain states expressed across local, interhemispheric and circadian scales, with implications for tracking dystonic state transitions and developing future state-aware adaptive neuromodulation strategies.

Disclosures: A. Balachandar: None. **K. Mithani:** None. **T.H. Latypov:** None. **S. Coleman:** None. **C. Gorodetsky:** Other; Received honoraria and/or research support from Abbott, Boston Scientific, and Medtronic. **G. Ibrahim:** Other; Received honoraria and/or research support from Abbott, Boston Scientific, and Medtronic..

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR317.21/DD14

Topic: F.03. Basal Ganglia

Support: T32 GM144300
R35NS132213

Title: Opto-inspired burst DBS engages downstream networks distinct from conventional DBS

Authors: *I. A. SALAS-ALLENDE[1], A. H. GITTIS[2];
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Abstract: Deep brain stimulation (DBS) is an effective therapy for Parkinsonian motor symptoms, but conventional high-frequency stimulation typically provides benefit only while stimulation is delivered. Our lab previously showed that cell-type-specific manipulation of external globus pallidus circuitry can produce locomotor recovery in dopamine-depleted mice that persists for hours after stimulation ends. This work led to an opto-inspired burst DBS pattern that uses brief, intermittent stimulation of the entopeduncular nucleus (EPN), the rodent homolog of the internal globus pallidus, to induce durable motor rescue with reduced total stimulation time. However, it remains unclear whether burst and conventional DBS act through overlapping or distinct circuits. To address this question, we used c-Fos activity mapping to compare network activity across dopamine-depleted mice receiving burst DBS, conventional DBS, or no

stimulation, as well as dopamine-intact no-stimulation controls. Behaviorally, burst DBS produced a gradual recovery of locomotion during stimulation that persisted after stimulation ended, whereas conventional DBS produced an acute rescue that rapidly returned to baseline after stimulation offset. Consistent with this behavioral dissociation, c-Fos analyses suggest that burst and conventional DBS recruit distinct circuits. For example, burst DBS was associated with increased c-Fos+ cell density in medial substantia nigra pars reticulata (SNr), which was not observed in conventional DBS or no-stimulation groups. In contrast, conventional DBS showed greater c-Fos+ density in primary motor cortex (M1) and the superior colliculus. We also observed differential inferior colliculus recruitment, with burst animals showing c-Fos+ cells in the dorsal inferior colliculus and conventional animals showing more prominent activity in the central inferior colliculus. Together, these findings suggest that burst DBS may drive persistent motor rescue by engaging distinct downstream networks. Defining these networks may inform circuit-guided DBS strategies that provide longer-lasting benefit while reducing total stimulation burden in Parkinson's disease.

Disclosures: I.A. Salas-Allende: None. **A.H. Gittis:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

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Topic: F.03. Basal Ganglia

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NIH NINDS 2R01NS097762-06A1 to PAF
NIH NINDS R00NS112417 to RCE
MJFF-028459 to RCE

Title: Sensorimotor integration via superior colliculus connections to the pedunculopontine nucleus

Authors: *B. J. BERNSTEIN, M. E. BARTLETT, P. A. FORCELLI, R. C. EVANS; Georgetown Univ., Washington, DC

Abstract: Sensory-motor integration in the brainstem is crucial for daily functioning and ultimately survival. Two structures involved in this process are the pedunculopontine nucleus (PPN) and the superior colliculus (SC), both of which are highly interconnected with basal ganglia nuclei. The PPN is a heterogeneous structure that is critical for sleep, arousal, and motor function and is implicated in both Parkinson's disease (PD) and epilepsy. Stimulation of the PPN is therapeutic in animal models of both disorders with a topography that is specific to cell type and location. The SC is important for integrating multisensory inputs to trigger motor responses, but the effect of SC projections to subregions and different cell types of the PPN is unknown. To address this gap in knowledge, we injected channelrhodopsin (ChR2) into the SC of ChAT-

Cre/Ai9, Vglut2-Cre/Ai9, and Vgat-Cre/Ai9 (tdTomato) mice to determine functional connectivity between SC synaptic inputs to PPN subpopulations using optogenetics and whole-cell patch clamp recordings in *ex vivo* brain slices. We find that almost all cholinergic and glutamatergic PPN neurons recorded receive excitatory synaptic input from the SC compared to around 75% of GABAergic PPN neurons. Since these cell types also show diverse motor effects across the rostral-caudal axis of the PPN, we separated this data into rostral and caudal subgroups. While the SC excites all three PPN cell types, the SC most strongly excites caudal cholinergic PPN neurons, as measured by the amplitude of excitatory postsynaptic currents. Furthermore, the SC drives firing in all PPN subpopulations, leading to depolarization block in a subset of glutamatergic and GABAergic neurons. Surprisingly, we also find inhibitory inputs from the SC to the PPN in around 40% of cholinergic and glutamatergic cells compared to just 26% of GABAergic cells. To determine what this means in an intact circuit, we optogenetically activated SC axons while recording from each PPN neuronal subtype using *in vivo* fiber photometry. We find that the PPN GABAergic calcium activity increases the most upon optogenetic stimulation of SC axons and habituates across trials. During stimulation, we find a decrease in distance traveled and mean speed and an increase in contralateral rotations. Given the important role the PPN plays in regulating arousal states and motor function, uncovering how the PPN responds to different inputs from the SC is important in understanding the modulation of movement in response to sensory stimuli.

Disclosures: B.J. Bernstein: None. **M.E. Bartlett:** None. **P.A. Forcelli:** None. **R.C. Evans:** None.

Poster

PSTR317: Basal Ganglia: Physiology and Plasticity

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR317.23/DD16

Topic: F.03. Basal Ganglia

Support: NIH/NIDA R01 DA056113

Title: Estradiol Modulation of Striatal Synaptic Plasticity

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Abstract: Estradiol regulates learning and impairs synaptic plasticity in the striatum, but its cell-type-specific mechanisms in the striatum remain unclear. Given the dorsal striatum's role in habit formation and substance use disorders, these findings suggest that estradiol-dependent suppression of plasticity may bias behavior from goal-directed to habitual. Because D1 and D2-spiny projection neurons (SPNs) differentially regulate action selection and behavioral strategies, the present study investigates how estradiol modulates synaptic plasticity within D1 & D2-SPNs

in the striatum. Methods: We used whole-cell patch-clamp recordings in SPNs in *ex vivo* brain slices in Drd1a-tdTomato mice. SPN identity was confirmed using intrinsic electrophysiological properties, and neuron subtype was identified based on fluorescence: D1-SPN (tdTomato +ve) or D2-SPNs (tdTomato -ve). EPSP amplitude was measured twice per minute before and after theta-burst stimulation (TBS) of corticostriatal afferents. To evaluate the effect of estradiol, ovariectomy was performed at postnatal day 42 (P42), and females were implanted with either estradiol or placebo pellets. Recordings were conducted after P52. Intact males were age-matched to females at the time of recording. Results: Preliminary studies showed a reduction in LTP in females treated with estradiol (FE) when compared to their placebo controls (FC) and males (M). In D1-SPNs, robust LTP was observed in M (238.0±64.2%, n=12) and FC (160.0±37.5%, n=8), when compared to FE (113.0±28.6%, n=5) at 20 min. This hierarchy was maintained at 30 min (M: 247.7±72.6%, n=11; FC: 155.3±40.6%, n=8; FE: 125.4±32.2%, n=5). In D2-SPNs, a matching suppression was observed at 20 min (M: 135.1±11.2%, n=3; FC: 185.9±81.6%, n=5; FE: 112.1±1.8%, n=2) with responses trending closely toward baseline across all groups by 30 min. Conclusion: These findings provide preliminary evidence that estradiol suppresses LTP uniformly across both striatal projection pathways, suggesting sex-specific modulation of synaptic changes within goal-directed dorsal striatal circuits. These results provide novel cell-type-specific insights into how ovarian hormones modulate striatal circuitry and may help explain sex-dependent vulnerability to habit-based neuropsychiatric conditions, including substance use disorders.

Disclosures: R. Rajan: None. **K.L. Blackwell:** None.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR318.01/DD17

Topic: F.05. Brain-Machine Interface

Support: NIH UH3NS107714
NIH R35 NS122333
Chalmers Area of Advance Health Engineering 2026

Title: Biomimetic microstimulation strategies for restoring natural touch in brain-controlled bionic hands

Authors: *M. CATTABRIGA[1], F. ANDOLFI[2], E. SEMENOVA[2], N. SHELCHKOVA[3], C. M. GREENSPON[4], G. VALLE[2];
[2]Dept. of Electrical Engin., [1]Chalmers Univ. of Technol., Gothenburg, Sweden; [4]Dept. of Organismal Biol. & Anat., [3]Univ. of Chicago, Chicago, IL

Abstract: Dexterous object manipulation critically relies on touch, which provides information about contact location and object properties. Somatosensory feedback continuously guides motor

commands and fine hand control. Its loss severely impairs motor performance, making restoration of touch critical for people with sensory deficits. Bidirectional brain-computer interfaces(BCIs) using intracortical microstimulation(ICMS) of the somatosensory cortex(SC) aim to restore touch and improve bionic hand control. Although ICMS-evoked sensations can enhance object interaction, they remain less natural than biological touch, limiting their functional impact. Recent biomimetic approaches have sought to better mimic natural tactile neural activity, demonstrating more natural sensations than conventional paradigms. However, generating both naturalistic and informative tactile percepts remains challenging, requiring a deeper understanding of SC touch encoding. In this study, we recorded neural activity from SC and motor cortex in a participant chronically implanted with intracortical NeuroPort electrodes and residual sensation in his contralateral hand. Controlled mechanical indentations were applied to individual digits using different indentation depths and rates. Multiunit activity was analyzed to characterize spatiotemporal dynamics. We observed robust SC responses modulated by indentation parameters, with firing rates and area of activation showing onset, sustained, and offset responses, consistent with previous observations in monkeys. Both indentation depth and rate significantly shaped these responses, with higher rates eliciting stronger but shorter onset activity, and higher depths increasing the overall response magnitude. Based on these findings, we designed ICMS stimulation patterns reproducing key aspects of the observed cortical dynamics using two biomimetic encoding strategies. The first encoder generated stimulation pulses directly from the participant's neural activity, providing a subject-specific approach. The second relied on a model estimating cortical activity from mechanical stimuli, providing a model-based encoding strategy that could potentially generalize across completely deafferented participants. Preliminary testing showed that biomimetic ICMS patterns were perceived as more realistic than conventional stimulation, supporting biologically inspired encoding strategies to improve naturalness and functional utility of artificial touch in bidirectional BCIs. Data were collected as part of a clinical trial conducted under an FDA Investigational Device Exemption(NCT01894802).

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Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Halls A-C

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Program #/Poster #: PSTR318.02/DD18

Topic: F.05. Brain-Machine Interface

Support: STI 2030-Major Projects (2022ZD0212300)

Title: Linguistically guided sentence-level tonal speech synthesis from human cortical activity

Authors: *X. HAO[1,2,3], P. YANG[4], Y. ZHOU[2,3], J. WU[1,2,3], Y. LI[3,4], J. LU[1,2,3];
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Abstract: Brain-to-voice neuroprostheses have the potential to decode neural activity directly into audible speech, enabling patients with speech loss to regain both verbal communication and essential paralinguistic features, such as vocal timbre and prosody. However, recent high-performance brain-to-voice BCIs have focused predominantly on non-tonal languages, whereas direct sentence-level synthesis in tonal languages like Mandarin, characterized by low phonetic redundancy and lexically contrastive tones, remains an open challenge. Here we developed a unified Conformer-based multi-task learning framework and validated it on electrocorticography (ECoG) data from seven participants, achieving direct sentence-level speech synthesis for Mandarin. In the closed-set task, acoustic feature regression successfully synthesized intelligible sentence-level tonal speech, with a participant-averaged median Pearson correlation coefficient (PCC) of 0.820, Mel-cepstral distortion (MCD) of 4.18 dB, and character error rate (CER) of 19.9%. For an open-set task with a comprehensive vocabulary of over 400 syllables, we found that jointly optimizing acoustic feature regression with linguistic unit classification substantially improved synthesis accuracy on unseen sentences compared to acoustic regression alone (median PCC: 0.79 vs. 0.77; MCD: 6.40 vs. 6.61 dB; CER: 62.8% vs. 76.2%, $P < 0.001$). This improvement was driven by the model establishing clearer higher-order phonetic category boundaries in its latent space and thereby significantly enhancing phonetic separability. Furthermore, to address practical clinical demands, we also implemented low-latency streaming decoding and applied transfer learning to enhance generalization when training data were limited. This study establishes the technical feasibility of direct sentence-level tonal speech synthesis from human cortical activity, representing a key step toward clinical brain-to-voice neuroprostheses for patients who speak tonal languages.

Disclosures: X. Hao: None. **P. yang:** None. **Y. Zhou:** None. **J. Wu:** None. **Y. Li:** None. **J. Lu:** None.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

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Topic: F.05. Brain-Machine Interface

Support: Alchemist Project (20012355, Fully implantable closed loop Brain to X for voice communication) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

Title: Generative Model-Based Neural-to-Speech Synthesis Using Confidence-Weighted Phoneme Decoding Outputs

Authors: *Y. GWON[1], E. LEE[2], C. CHUNG[3];
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Abstract: Restoring intelligible speech from neural activity is a key goal of speech brain-computer interfaces. Recent studies have reconstructed text, phonemes, acoustic features, and waveforms from invasive recordings, but many pipelines reduce neural activity to a deterministic phoneme or word sequence before synthesis. This discards decoder confidence, although decoding errors are inevitable and neural evidence is subject-specific and constrained by sparse electrode coverage. We proposes a confidence-aware neural-to-speech framework based on flow matching with element-wise classifier-free guidance. Neural activity was recorded from one participant with drug-resistant epilepsy using stereoelectroencephalography during a Korean sentence repetition task. Signals were converted into frequency-band envelopes, and phoneme elements were decoded with multiclass logistic regression. Each Korean syllable was decomposed into onset, nucleus, and coda elements, yielding posterior probabilities over candidate phonemes. To use these probabilities, the model represents each word as phonological elements and learns full-condition and single-element conditions. At inference, guidance directions are computed for candidate phonemes and mixed by decoder probabilities. This element-wise mixture guidance conditions speech generation on uncertain neural outputs probabilistically, instead of collapsing them into an argmax sequence. Phoneme decoding was significant across most frequency-band conditions, with the lowest error rate when all bands were combined. In speech generation, both full and element-wise guidance outperformed shuffled baselines. Element-wise mixture guidance did not outperform full guidance overall, but reduced mel-cepstral distortion in better decoded samples, suggesting the benefit of confidence-weighted guidance when neural decoding is relatively reliable. Overall, this work introduces a flow matching-based neural-to-speech pipeline that preserves phoneme-level decoder uncertainty through confidence-weighted guidance. The results support a flexible framework for speech BCIs operating with incomplete, error-prone, and spatially limited neural evidence.

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Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

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Program #/Poster #: PSTR318.04/DD20

Topic: F.05. Brain-Machine Interface

Support: NIH NIDCD R21 DC021013

Title: Mapping intracranial EEG to semantic embedding spaces with a deep transformer decoder

Authors: *W. L. GROSS[1], A. SKITOWSKI[2], S. MATHEW[3], D. AHMED[4], H. G. REY[5], K. GUPTA[5], A. ANDERSON[6];
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Abstract: Although neuroprosthetic research has largely focused on motor BCIs, people with severe aphasia typically retain motor output and instead require systems that decode intended meaning directly. Here, we tested whether single-trial sEEG activity during semantic categorization of concrete-object images could be decoded into a semantic embedding space. Five patients viewed multiple image exemplars from 20 concrete concepts across 3,000 trials. Neural signals were decomposed into canonical EEG frequency bands and decoded using either a ridge-regression encoder or a deep transformer decoder. The transformer architecture included convolutional tokenizer layers, axial transformer layers, and an MLP readout. Performance was evaluated by mean percentile rank (MPR; chance = 0.5) across three held-out stimulus sets: RepeatImage, held-out presentations of trained images; CrossExemplar, novel images of trained concepts; and NovelConcept, concepts excluded from training.
Both models decoded semantic embeddings above chance, although the transformer outperformed ridge regression overall (MPR, 0.574 vs. 0.538; $p < 0.001$). The transformer also outperformed ridge regression for RepeatImage decoding (0.625 vs. 0.536; $p < 0.001$) and CrossExemplar decoding (0.627 vs. 0.547; $p < 0.001$). In contrast, both models generalized poorly to NovelConcept stimuli, with no significant difference between models (0.5302 vs. 0.5155; $p = 0.135$).
Model-lesion analyses indicated that axial decoding depended primarily on high-gamma and alpha-band activity 180-370 ms after stimulus presentation, with large contributions from inferior and lateral temporal lobe contacts, particularly in the fusiform gyrus. Lesion effects showed no reliable hemispheric dominance. Trial-scaling analyses suggested that transformer decoding improved with additional data, particularly above 16 trials per concept. Dimensional-scaling analyses indicated that the available input data supported reliable decoding only up to a four-dimensional semantic space.
These findings demonstrate that semantic embeddings can be decoded from iEEG activity and that performance improves with nonlinear, high-capacity models. Limited trial counts and electrode coverage remain key constraints for semantic language BCIs.

Disclosures: W.L. Gross: None. **A. Skitowski:** None. **S. Mathew:** None. **D. Ahmed:** None. **H.G. Rey:** None. **K. Gupta:** None. **A. anderson:** None.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR318.05/DD21

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01EB023261
JWMRP Grant W81XWH1910839

Title: Enabling prosthesis users to identify the physical properties of a grasped object using multi-channel peripheral nerve stimulation

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Abstract: Users of myoelectrically controlled prosthetic hands report high reliance on visual and auditory attention during everyday tasks due to the absence of tactile feedback. This reduces the ability to process information related to hand aperture and applied grip force. Thus, increasing the risk of unintentional accidents (i.e. crushing an object) and higher cognitive strain, which contributes to system abandonment. We have developed a neural-enabled prosthetic hand (NEPH) system that integrates a sensorized prosthetic hand, prosthesis-mounted electronics, a wirelessly controlled implanted neurostimulator, and a set of intrafascicular electrodes in the median and ulnar nerves to elicit task-relevant sensations referred to the phantom hand. Stimulation pulse sequences are delivered to a set of electrodes based on real-time information derived from one or more sensors in the prosthetic hand. For example, sensors that detect information related to grasp force can drive stimulation to one or more electrodes, while sensors that measure hand aperture can drive stimulation to other electrodes. We are conducting a first-in-human clinical trial (ClinicalTrials.gov ID: NCT03432325) to evaluate the safety and utility of stimulation-induced sensory feedback over a two-year post-implant participation period. Here, we assessed the ability of NEPH system users to identify physical properties of grasped objects. Participants used industry-standard EMG control to operate a prosthetic hand that was mechanically isolated from the residual limb and mounted on a tripod. Vision and auditory cues were eliminated using a curtain and headphones with white noise. Sensory feedback was provided via electrical stimulation within parameters that were comfortable and meaningful to each participant. Objects varying in size and compliance (large-hard, large-soft, small-hard, small-soft) were presented for grasping, after which the participant identified the object properties. In each session, each of the four objects was presented six times in a randomized order, divided into two blocks. Results from five participants show performance above chance when two stimulation channels with distinct perceptual characteristics and graded intensity were provided. In some cases, higher percept clarity of the two electrodes was associated with improved performance within the participants. These findings support the use of multi-channel sensory feedback to convey object properties and suggest potential to reduce reliance on visual and auditory attention, improving functional use of upper-limb prostheses and quality of life.

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Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

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Topic: F.05. Brain-Machine Interface

Support: R01-EB027584
R01-EB023261

Title: Tool for peripheral nerve stabilization during surgery

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Abstract: Neurosurgical procedures involving nerve manipulation, including implantation of electrodes within peripheral nerves, are technically challenging because of the delicate anatomy of peripheral nerve tissue, the need for stable intraoperative positioning, and the difficulty of accessing individual fascicles. We developed a novel surgical tool to stabilize the peripheral nerve and align the fascicles to facilitate smoother and more efficient intrafascicular electrode implantation. The device consists of a raised flat platform with sloped sides and a grooved channel at each edge extending across its width. Positioned beneath the nerve, the platform works with vessel loops placed across the grooves to stabilize and partially flatten the nerve, improving access while reducing handling. The tool can be scaled during fabrication to accommodate nerves of different sizes. Its performance was evaluated during implantation of longitudinal intrafascicular electrodes (LIFEs) made from 23 μm Pt/Ir wires attached to a 75 μm tungsten needle used to thread the electrode through a fascicle. Testing was conducted in *in-vivo* studies in anesthetized rats (70 sciatic nerves) and pigs (6 vagus nerves), with one to four electrodes implanted per fascicle. Use of the tool reduced nerve torsion, minimized the need for forceps and other manipulations during LIFE placement, decreased procedural difficulty, decreased implantation time by more than half, and improved overall efficiency. The nerves showed minimal resistance to needle passage during implantation. Visual nerve inspection during use indicated preserved blood perfusion without apparent neural tissue color change and in relation to the proximal aspect of the nerve. After electrode placement and tool removal, high-density epimysial electromyograms recorded from a 32-channel grid placed on the gastrocnemius lateralis muscle showed robust evoked responses during repeated sciatic nerve stimulation, with expected strength-duration curves maintained for up to 10 hours. Similarly, robust respiratory responses were observed during vagal nerve stimulation up to 5 hours after tool removal. The tool was also tested in cadaver studies for implantation into the human medial and ulnar nerves. A medical-grade stainless-steel version received investigational device exemption approval from the U.S. Food and Drug Administration for LIFE implantations. This surgical tool could improve the deployment of intrafascicular peripheral nerve interfaces, enhance nerve surgery, and broaden options for nerve grafting, nerve repair, and even end-to-end vascular anastomosis.

Disclosures: A. Ortega Sanabria: None. **A. Holmes:** None. **A.K. Thota:** None. **J.J. Abbas:** None. **R. Jung:** None.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

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Program #/Poster #: PSTR318.07/DD23

Topic: F.05. Brain-Machine Interface

Support: NIH Grant EY023336

Title: To see or not to see: Neural activity before and after visual cortex stimulation in human sEEG patients

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Abstract: Electrical stimulation of human visual cortex can evoke a visual sensation akin to a flash of light, termed a phosphene. Visual cortical prostheses (VCPs) combine phosphenes to convey useful visual information. To ensure the long-term safety and efficacy of VCPs, it is desirable to minimize the current delivered at each electrode. However, at low currents, stimulation sometimes produces a phosphene and sometimes does not. We examined the neural correlates of probabilistic phosphene perception in three epilepsy patients implanted with stereotactic EEG (sEEG) electrodes in visual cortex. Neighboring contacts were used for stimulation and recording to measure neural activity related to phosphene production. First, electrode contacts in early visual cortex (V1, V2, V3) were stimulated to find those that reliably produced phosphenes. Current levels were reduced until phosphenes were reported on approximately half of trials. In each experimental trial, 100ms, 200Hz pulse trains were delivered to the selected electrode. Patients reported perception with a button press. A total of four electrodes in three patients were stimulated. Patients reported a phosphene on 57% of trials (mean of 123 stimulation trials, mean current 0.48mA). First, we examined the event-related potential in the electrode adjacent to the stimulating electrode. The evoked response peaked at 128ms following stimulation onset and was significantly larger in trials for which the participant reported a phosphene (percept trials). Next, we examined the spectral properties of the stimulation-evoked response. Percept trials had a larger increase in broadband high-frequency activity (BHA, 50-150 Hz) in the period shortly after stimulation onset (50-250ms). Finally, we examined neural activity *before* stimulation to determine if phosphene perception was related to ongoing activity. There was lower power in the alpha band (8-12 Hz) from approximately 750ms before stimulation onset in "percept" compared to "no percept" trials. Perception of phosphenes was associated with distinct patterns of neural activity *before* and *after* stimulation. Post-stimulation, perception was linked to larger evoked responses (reflecting summed synaptic potentials) and BHA (population activity). Pre-stimulation, phosphene perception was correlated with weaker alpha activity, consistent with prior work indicating that alpha power indexes visual cortex excitability. A better understanding of these neural features may inform stimulation strategies for VCPs that minimize current requirements while improving reliability, safety and device longevity.

Disclosures: S. Kang: None. **D. Oswalt:** None. **M. Beauchamp:** None. **H.I. Chen:** None. **D. Yoshor:** None.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

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Program #/Poster #: PSTR318.08/DD24

Topic: F.05. Brain-Machine Interface

Support: R01EY036094
R01NS102917

Title: Ultraflexible Bidirectional Electrodes for Thalamic Visual Prosthetics

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Abstract: Electrical visual prostheses have demonstrated that microstimulation can restore rudimentary visual perception, providing an important foundation for artificial vision. Retinal and cortical approaches have advanced this field substantially, but their applicability remains limited by disease-specific constraints and unresolved challenges in achieving broad visual field coverage and long-term biocompatibility. The lateral geniculate nucleus (LGN) is a compact, retinotopically organized thalamic relay that represents the full visual field within a small deep-brain structure, making it an attractive target for visual restoration. At the same time, its small size and compact structure impose strict requirements on the tissue-probe interface. Additionally, how LGN microstimulation modulates local neural circuits, how stimulation-evoked activity relates to visual organization, and whether this organization is preserved after blindness remain insufficiently understood.Here, we evaluate the feasibility of developing a durable LGN visual prosthesis using high-density, bidirectional ultraflexible Nanoelectronic Threads (NETs) in mice, while establishing key knowledge of longitudinal neural dynamics in the LGN and V1 before and after blindness. We demonstrate that NETs provided stable single-unit recordings and functional mapping in the LGN over many months, indicating a stable tissue-electrode interface. Microstimulation through NETs elicited spatially localized neuronal recruitment within approximately 100 μm of the stimulation site and temporally precise modulation at frequencies up to 100 Hz. The frequency- and current-dependent responses of recruited neurons remained stable over time. Following the induction of blindness, microstimulation using the same stimulation parameters recruited a comparable number of neurons and produced similar gain modulation. Based on visual response properties measured before blindness, these findings suggest that LGN microstimulation can evoke comparable phosphene percepts before and after vision loss. In a separate cohort of GCaMP6s mice, we performed calcium imaging in V1 during LGN microstimulation before and after blindness. LGN stimulation evoked similar patterns and magnitudes of cortical activation under both conditions, providing additional support for the stability of stimulation-evoked visual representations following vision loss. Together, these

findings demonstrate the feasibility of stable, long-term thalamic visual prostheses and highlight the LGN as a promising target for vision restoration.

Disclosures: Y. Sun: A. Employment/Salary (full or part-time):; Rice 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.; R01NS102917, R01EY036094. **R. Yin:** A. Employment/Salary (full or part-time):; Rice University. **P. Zolotavin:** A. Employment/Salary (full or part-time):; Rice University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuralThread Inc. **X. Zhang:** A. Employment/Salary (full or part-time):; Rice University. **Y. Liu:** A. Employment/Salary (full or part-time):; Rice University. **P.R. Roelfsema:** None. **C. Xie:** A. Employment/Salary (full or part-time):; Rice University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuralThread Inc. **L. Luan:** A. Employment/Salary (full or part-time):; Rice 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.; R01NS102917, R01EY036094. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuralThread Inc.

Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Halls A-C

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Program #/Poster #: PSTR318.09/DD25

Topic: F.05. Brain-Machine Interface

Support: NRF Grant 2022M3C1A3081294

Title: Fully Noninvasive Closed-loop Transcutaneous Tibial Nerve Stimulation System for Bladder Control via Pupillometry

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Abstract: Non-invasive electrical neuromodulation is emerging as a promising alternative to pharmacological treatments for neurogenic disorders. However, transcutaneous stimulation often leads to irregular current delivery, resulting in inconsistent activation of target nerves and reduced therapeutic reliability. To overcome these limitations, a closed-loop (CL) neuromodulation system capable of monitoring stimulation-induced physiological changes and dynamically adjusting stimulation intensity is required. Despite this need, feedback variables

suitable for non-invasive systems remain insufficiently defined. In this study, we propose pupillometry — which reflects the neural activity of the Locus Coeruleus, the micturition center — as a feedback biomarker for a non-invasive CL neuromodulation system, and apply it to a therapeutic system for bladder dysfunction. All experiments were conducted under the approval of the Institutional Animal Care and Use Committee (IACUC) of POSTECH, using male Long-Evans rats aged 8-12 weeks (POSTECH-2025-0099). Through data-driven analysis using time-series methods, a strong correlation between pupil dynamics and voiding was confirmed (Pearson correlation coefficient, median [Q1, Q3]: 0.71 [0.65, 0.87], n = 6). Pupil dilation was found to begin 7 seconds (median [Q1, Q3]: 7 [4, 20], n = 6) prior to voiding, with a 3.2-fold (median [Q1, Q3]: 3.7 [3.2, 5.0]) expansion relative to baseline. Furthermore, strong linear correlations were observed between maximum voiding contraction pressure and both the magnitude and rate of pupil dilation. These findings suggest that pupil dilation can serve as a reliable biomarker for monitoring voiding patterns. Building on this potential, we implemented a CL neuromodulation system integrating pupillometry with transcutaneous tibial nerve stimulation — a safe and non-invasive therapeutic approach currently under investigation for bladder dysfunction — and evaluated it in a rat model (n = 6). The proposed system successfully diagnosed frequent micturition events — induced by increasing the saline infusion rate — by tracking the rapid pupil dilation associated with voiding. When multiple sub-baseline frequent micturition events occurred, tibial nerve stimulation successfully extended the inter-micturition interval by 24.5%. These results demonstrate that pupillometry can function as an effective feedback variable and demonstrate the feasibility of implementing a fully non-invasive CL neuromodulation system capable of precise and adaptive control, representing a promising therapeutic target for voiding dysfunction such as frequent micturition.

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Poster

PSTR318: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Halls A-C

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Program #/Poster #: PSTR318.10/DD26

Topic: F.05. Brain-Machine Interface

Title: Demographic Representation in Brain-Computer Interface Studies for Motor Recovery and Pain-Related Outcomes: A Bibliometric Analysis of Neurological and Motor Impairment Populations

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Abstract: Brain-computer interfaces (BCIs) are a rapidly evolving neurorehabilitation modality; advancements depend on the demographic and methodological rigor of foundational research. This study conducts a bibliometric and demographic analysis of the 100 most-cited BCI studies related to motor recovery and pain management, extracted from Web of Science on March 4, 2026, covering recent publications from 2010-2026. Following PRISMA 2020 guidelines, articles were screened and excluded if they were review articles or outside defined clinical scope, yielding 20 articles for in-depth analysis, while the full corpus was retained for trend analysis using RStudio and Excel. This study is limited by lack of research into a causal relationship between representational gaps and mechanistic outcomes.
Authorship clusters shows (1) foundational BMI feasibility work, (2) clinical motor recovery in stroke and SCI, (3) mechanistic and user-performance studies, (4) pain-related therapeutic applications, (5) preclinical closed-loop neuromodulation, and (6) biomarker work in CNP and SCI populations. Demographic underrepresentation and lack of population reporting was pronounced; race was unreported in 99 of 100 articles. Among the 20 included studies, sex was specified for 183/244 participants (75%), with 73.2% identified as male. 11/20 studies employed proof-of-concept, pilot, case, longitudinal, cross-sectional, or observational design; only 3 were RCTs; 12 had $n \leq 20$ participants. This is a technical liability, as BCIs depend on neural decoding algorithms trained with physiological data. Underrepresentation of women risks neglecting sex-based hormonal differences in synaptic plasticity. Absence of race reporting obscures population-level differences in signal acquisition constraints, such as electrode-scalp impedance variation linked to hair texture and skin tone that affect BCI performance. Going forward, advancing equitable BCI development will require standardized demographic reporting and increased inclusion of diverse participants with adoption of randomized controlled trial designs.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR319.01/DD27

Topic: F.09. Motor Neurons and Muscle

Support: AICoS project (CUP B79J23000340005) supported by Italian Ministry of Economic Development (MISE)

Title: Scalable Multi-Omics Phenotypic Profiling in Human iPSC-Derived Motor Neurons for Functional Genomics and Target Discovery

Authors: P. BONETTI[1], D. PRESUTTI[1], R. RAVASIO[1], D. BARDELLI[1], I. COTELLESSA[1], S. MARTIN[1], S. CAINARCA[1], K. HEADLAND[1], *J. ROLLAND[1], **H. SHAW**[2], F. RICCI[1]; [1]Axxam SpA, Bresso, Italy; [2]Business Develop., Axxam Inc., Cambridge, MA

Abstract: Emerging clinical and omics-driven datasets reveal persistent gaps between molecular complexity and therapeutic outcomes, underscoring the urgent need to identify new, mechanistically precise targets in neuroscience to better address unmet needs. Axxam have therefore developed a target discovery platform leveraging CRISPRKO-ready induced pluripotent stem cell (iPSC)-derived human motor neurons to enable functional interrogation of gene targets in a neuronal disease-relevant context. We performed an arrayed CRISPR knockout screen to systematically investigate gene function and identify modulators of cellular phenotypes in human iPS-derived motor neurons. To capture a comprehensive view of gene perturbation effects, the screening workflow was coupled with two complementary multi-omics readouts, high-content morphological profiling (Cell Painting) and transcriptomic analysis (DRUG-seq). This integrated approach allowed us to link genetic perturbations to both phenotypic and molecular signatures, providing a multidimensional framework for target identification and validation. The entire screening campaign was performed in a miniaturized 384-well plate format using fully automated screening station and automated liquid handlers, demonstrating the scalability and robustness of the platform. Preliminary analyses indicate that high-content imaging can capture distinct perturbation-associated phenotypes and provide biologically meaningful insights that complement molecular profiling approaches. Overall, this work highlights the value of combining CRISPR-based functional genomics, advanced human cell models, high-content imaging, and transcriptomics to support target discovery and validation. The platform provides a scalable framework for investigating gene function, accelerating and generating human relevant disease models for drug discovery efforts in neurological disease research.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

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Program #/Poster #: PSTR319.02/DD28

Topic: F.09. Motor Neurons and Muscle

Support: R01NS091575
R56NS134237

Title: SMN deficiency induces a NEAT1 mediated inflammatory pathway that promotes microglial dysfunction

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Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by reduced expression of the survival motor neuron (SMN) protein. In addition to motor neuron degeneration, SMA microglia exhibit reactive inflammatory phenotypes characterized by complement activation and aberrant phagocytosis. However, the molecular mechanisms linking SMN deficiency to pathological microglial dysfunction remain poorly understood. Defining these pathways may uncover novel disease modifying mechanisms and therapeutic targets in SMA. In this study, we utilized human iPSC derived microglia and a doxycycline inducible CRISPRi model to investigate if SMN deficiency acts as a cell autonomous trigger for microglial reactivity. We performed transcriptome analysis, combining topology based Signaling Pathway Impact Analysis with functional class scoring against multiple databases to identify high confidence disease pathways. We further validated the identified pathways via SMN restoration, genetic ablation, and pharmacological inhibition of target subunits.
Results revealed that SMN deficient microglia significantly upregulate immune pathways, specifically antigen processing, cross presentation, and the complement system. SMN deficiency was sufficient to induce the immunoproteasome. Mechanistically, we identified long noncoding RNA (lncRNA) NEAT1 as a novel upstream regulator of this inflammatory state. NEAT1 repression reduced STAT1 phosphorylation and immunoproteasome induction, establishing a previously undefined link between lncRNA biology and immunoproteasome assembly. Functionally, SMN deficiency selectively disrupted complement mediated microglial phagocytosis, reducing C1q dependent phagocytosis while largely sparing iC3b mediated phagocytosis. Partial restoration of C1q mediated phagocytosis following NEAT1 repression links this newly identified inflammatory pathway to disease relevant microglial dysfunction in SMA.
These findings reveal a novel inflammatory axis in SMA microglia where SMN deficiency induces a “pseudo viral” state driven by NEAT1 and immunoproteasome activity. This suggests that NEAT1 acts as an upstream regulator of STAT1 signaling and immunoproteasome assembly, offering a potential therapeutic target to reduce microglial reactivity. Furthermore, the discrepancy between increased C1q production and decreased C1q phagocytic efficiency highlights a complex role for the complement system in SMA pathology.These pathways provides new mechanistic insights into the nonneuronal contributions to SMA and suggests that the immunoproteasome and NEAT1 could serve as viable disease modifiers.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

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Topic: F.09. Motor Neurons and Muscle

Support: R01 NS078375 (GZM)
R01 AA027079 (GZM)
K01 1K01DE033040 (DFP)

Title: CD47 and C3 mediate inappropriate excitatory but not inhibitory synapses elimination on motor neurons in early development in mice

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Abstract: Proper assembly of sensory-motor circuits is fundamental to ensuring smooth overground movement in mammals. Previously, we reported that the complement proteins C1q and C3 are involved in the refinement of VGluT1 synapses during early development. Additionally, we reported that CD47, previously known as a "don't eat me" signal, also contributes to the elimination of VGluT1 proprioceptive synapses via microglial engulfment in the neurodegenerative disease spinal muscular atrophy (SMA). These mechanisms are important for eliminating inappropriate VGluT1+ synapse formation between proprioceptors and antagonistic muscles, thereby affecting motor behavior. However, it is unknown whether complement proteins and CD47 also affect other excitatory and inhibitory synapses in the spinal cord that are important for corticospinal descending pathways and the regulation of motor neuron activity via interneurons. To address this question, we studied the effect of C3 and CD47 deletion on VGluT2 excitatory synapses and GABAergic (GAD65/67+) inhibitory synapses during postnatal spinal cord development. We used mice at postnatal day 5 (P5), as this corresponds to the peak of synaptic pruning activity in the spinal cord. We performed immunohistochemistry experiments on the L4 spinal cord segment and analyzed individual motor neurons in knockout (KO) animals and their wild-type (WT) counterparts. Results revealed an increase in VGluT2+ synapses, but no changes in inhibitory synapses labeled with GAD65/67 antibodies (isoforms of the enzyme glutamate decarboxylase). Furthermore, we investigated whether the effect on VGluT2+ synapses was mediated by microglial activation. Quantification of microglia containing VGluT2 residues showed a significant decrease in C3 KO and CD47 KO mice compared to WT animals. However, the same analysis for GAD65/67 revealed no differences. These results suggest that C3 and CD47 participate in the refinement of excitatory synapses through microglial activity, while having no apparent effect on inhibitory synapses. Most importantly, we observed that microglia still contained GAD65/67 residues in all animals, indicating that the potential refinement of inhibitory synapses, if present, may be mediated by a different mechanism. Taken together, these findings raise the possibility that genetic elimination of CD47 and C3 could be used as a therapeutic target for sensory-motor disorders that specifically affect excitatory synapse formation.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

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Program #/Poster #: PSTR319.04/DD30

Topic: F.09. Motor Neurons and Muscle

Title: A spatially resolved single-cell transcriptomic and epigenomic atlas across macaque motor cortex subregions

Authors: Y. LEI[1], Q. CHAI[2], Z. ZHU[4], Z. WANG[5], L. DING[4], N. YUAN[6], ***Z. SHEN**[3];
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Abstract: We generated a high-resolution single-cell and spatial multi-omics atlas of the macaque motor cortex (subregions F1-F7) to investigate its cellular diversity and regional functional specialization. By integrating single-nucleus RNA sequencing (snRNA-seq), single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq), and spatiotemporal enhanced resolution omics-sequencing (Stereo-seq) datasets, we revealed marked regional differences in cellular composition, such as the high enrichment of oligodendrocytes in the primary motor cortex (F1) and the gradient distribution of layer 4 (L4)-like neurons across subregions. Furthermore, our multimodal analysis not only finely characterized the molecular and epigenomic features of primate-specific Betz cells—identifying a regulatory network centered on *TOX* and *ZBTB16*—but also revealed via spatially constrained clustering that layer 3 (L3) can be further subdivided into superficial (L3s) and deep (L3d) sublayers, which exhibit distinctly divergent cell-cell communication profiles. Collectively, this study provides a valuable foundational resource for understanding the organizational architecture and functional evolution of the primate motor cortex.

Disclosures: Y. Lei: None. **Q. Chai:** None. **Z. Zhu:** None. **Z. wang:** None. **L. Ding:** None. **N. Yuan:** None. **Z. Shen:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.05/EE1

Topic: F.09. Motor Neurons and Muscle

Support: NSF 2525492

Title: Premotor neuron selectivity as a potential contributor to orderly motor neuron recruitment

Authors: *D. FREEMAN, O. S. WADHWA, H. FU, J. AUSBORN;
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Abstract: Orderly recruitment of motor neurons (MNs) is essential for smooth, graded force production. Henneman's size principle states that smaller, higher-input-resistance MNs are recruited before larger, less excitable MNs as synaptic drive increases. However, recruitment may also depend on how premotor circuits distribute functional drive across MN classes. In *Drosophila*, slow, intermediate, and fast tibia flexor MNs are similarly recruited according to

Henneman's principle (Azevedo et al., 2020). Because slow and fast tibia flexor MNs share many premotor neurons (preMNs), we asked whether shared preMNs provide equivalent drive to both, or instead preferentially bias activation of specific MNs. To investigate this, we generated electron microscopy (EM) connectome-informed multicompartment models of identified slow and fast tibia flexor MNs and mapped synaptic inputs from shared preMNs onto reconstructed dendritic arbors. Models were constrained using published electrophysiological recordings (Azevedo et al., 2020). Using these models, we simulated excitatory postsynaptic potentials (EPSPs) evoked by shared preMNs to determine how premotor input structure contributes to MN depolarization. When all shared preMN synapses were activated simultaneously, slow and fast MNs reached similar peak depolarizations, despite differences in synapse number and intrinsic excitability, suggesting that total premotor drive may be balanced across MN classes. However, activation of individual shared preMNs revealed substantial selectivity: some preMNs preferentially depolarized the slow MN, whereas others preferentially depolarized the fast MN. These results suggest that anatomically shared premotor input does not necessarily produce equivalent functional drive and that preMN selectivity, together with intrinsic MN properties, may contribute to slow-to-fast orderly recruitment.

Disclosures: D. Freeman: None. **O.S. Wadhwa:** None. **H. Fu:** None. **J. Ausborn:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.06/EE2

Topic: F.09. Motor Neurons and Muscle

Support: R35NS142987
R01MH046742

Title: Synaptic Properties and Responses to Temperature and Neuromodulation in Two Muscles Innervated by the Same Neuron

Authors: *J. ZENG, K. JACQUERIE, E. E. MARDER;
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Abstract: Synapses innervated by a single neuron can have distinct properties, especially when targeting different muscles. We study two muscles, gm5b and gm6, innervated by the same neuron, LG, in the gastric mill of the crab Cancer borealis. We ask: How variable are LG synapses across muscle fibers, muscles, and animals? How similar or different are LG synapses onto different muscles responding to temperature changes and neuromodulator (allatostatin) application?
To characterize baseline synaptic properties (without synaptic plasticity) and plasticity at synapses on gm5b and gm6, we performed intracellular voltage recordings from muscle fibers while stimulating the lgn nerve with a designed stimulus pattern using a suction electrode. The

stimulus pattern included long inter-stimulus intervals to capture baseline synaptic responses and a wide range of intervals to capture synaptic plasticity. To quantify baseline properties and plasticity, we built a synapse-based model that fit the intracellular recordings and extracted the parameter set that best described each synapse under specific experimental conditions.
Although all synapses on gm5b and gm6 are innervated by the same LG neuron, they exhibit distinct properties. At 11°C, gm5b shows significantly larger EJP responses to single and burst stimuli, as well as higher facilitation time constants, presynaptic calcium removal time constants, vesicle refill time constants, depression time constants, and initial release probabilities than gm6. For example, the presynaptic calcium removal time constant typically ranges from 5-10 s in gm5b but only 3-4 s in gm6. Synaptic properties are also highly variable across fibers within the same muscle, although this variability is generally smaller than that observed across animals and between muscles. For example, for the single-stimulus response amplitude in gm5b, the standard deviation across fibers is ~2 mV, across animals ~3 mV, and the difference between muscle means ~6 mV.
Despite these differences, the two muscles show similar responses to temperature changes and to type A D-AST-3 (Diploptera allatostatin 3). As temperature increases, responses to single and burst stimuli, EJP decay time constants, presynaptic calcium removal time constants, and vesicle refill time constants all decrease in both muscles. With D-AST-3 application, responses to single stimuli and initial release probability decrease to ~70% of saline values, whereas responses to burst stimuli decrease only to ~90% in both muscles.

Disclosures: J. Zeng: None. **K. Jacquerie:** None. **E.E. Marder:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.07/EE3

Topic: F.09. Motor Neurons and Muscle

Title: Beyond Gain Control: Persistent Inward Currents as the Cellular Engine of Predictive Yield Compensation in Spinal Motoneurons

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Abstract: When a stretched muscle yields, actin-myosin cross-bridges fail within ~20 ms, a mechanical collapse too fast for any reactive reflex to correct. Fifty years ago, Houk, Crago, and Rymer demonstrated that the intact nervous system masks this yield before it occurs, a feedforward computation driven by the Ia afferent burst. The cellular mechanism that converts that afferent trigger into mechanical compensation has never been identified. We recently proposed (Chardon, Heckman & Rymer, *J Physiol*, 2026, https://doi.org/10.1113/JP287663) that

persistent inward currents (PICs) in spinal motoneurons are the engine of this predictive compensation, with the fast soma-proximal sodium PIC (NaPIC) masking the rapid yield event and the slow dendritic calcium PIC (CaPIC) sustaining force through the plateau. Here we report two findings from the unanesthetized decerebrate cat soleus preparation that directly support this framework. First, predictive compensation is velocity dependent: ramp-and-hold stretches across the locomotor range (30-100 mm/s, 10 mm amplitude) show that yield severity rises monotonically with stretch velocity, with full compensation at slow velocities and frank force reversal at high velocities, consistent with a predictive controller that is outrun as Ia discharge rates exceed the recruitment capacity of the motoneuron pool. Second, selective NaPIC blockade with intrathecal riluzole causes yield to re-emerge on the force trace at the 20-40 ms latency predicted by the classical yield window, reducing the dynamic peak by 61%, while the plateau is substantially preserved, reduced by only 47% and markedly more stable, consistent with CaPIC continuing to sustain force after NaPIC is removed. Together these results support a double dissociation: NaPIC masks the rapid yield, CaPIC maintains the plateau. This reframes PICs not only as gain controllers of motoneuron excitability, but as the intrinsic cellular component of a predictive mechanical controller, a distinction with direct implications for PIC dysregulation in spasticity, spinal cord injury, and ALS.

Disclosures: M.K. Chardon: None. **A. Mahrous:** None. **M.D. Johnson:** None. **C. Heckman:** None. **W.Z. Rymer:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.08/EE4

Topic: F.09. Motor Neurons and Muscle

Title: DECIPHERING THE DENDRITIC STRUCTURE OF PYRAMIDAL TRACT NEURONS ACROSS CORTICAL AREAS AND PROJECTION TARGETS IN THE MOUSE

Authors: *P. AHIRWAL, J. SCHILLER;
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Abstract: Layer 5 thick-tufted pyramidal tract (PT) neurons are the major output neurons of the neocortex, sending motor commands to directly drive behavior. PT neurons are heterogeneous and can be classified according to their molecular identity, projection targets, and functional specialization. We previously identified two morphologically and functionally distinct PT neuron subtypes in the mouse primary motor cortex. Type-1 neurons exhibit an early apical bifurcation, a long nexus, and compartmentalized tuft activation, whereas type-2 neurons exhibit a late bifurcation and a short nexus and more synchronous tuft activity. Here we investigate how type-1 and type-2 dendritic morphologies relate to the known PT neuron taxonomy across projection targets cortical areas. To address this question, we retrogradely labeled PT neurons projecting to the cervical spinal cord or thalamus and reconstructed their full apical dendritic morphology,

across several cortical regions including the primary motor cortex (M1), secondary motor cortex (M2), and somatosensory cortex (S1), as well as non-motor-related areas such as the anterior cingulate cortex (ACC). In a subset of neurons, we also performed whole-cell patch-clamp recordings to characterize the intrinsic properties associated with these morphological subtypes. Our retrograde tracing and morphological reconstruction data show that corticospinal M1 neurons are highly enriched for type-1 dendritic morphology, characterized by an early first tuft bifurcation, a long nexus, and deeper somatic location. In contrast, corticothalamic neurons are enriched for type-2 morphology, characterized by a later first tuft bifurcation, a shorter nexus, and a more superficial somatic location. These findings suggest that dendritic morphology is closely linked to projection targets and may represent an additional organizing principle of PT neuron identity. Together with molecular and projection-based classifications, dendritic architecture may help define the mode by which PT neurons integrate cortical information and transform it into motor output.

Disclosures: P. ahirwal: None. **J. Schiller:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.09/EE5

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant NS079147

Title: Blockade of persistent inward currents does not affect spinal motor unit activity during voluntary muscle contractions in rodents

Authors: *S. CHIN[1], N. W. CARLETON[1], H. C. BUFFINGTON[1], T. M. LARGENT-MILNES[2], R. ZANOTTI[4], F. NEGRO[5], A. J. FUGLEVAND[3];
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Abstract: Persistent inward currents (PICs) represent a neuromodulator (serotonin, noradrenaline) mediated intrinsic source of membrane depolarization. The added boost of depolarization provided by PICs can markedly amplify firing rates and even lead to self-sustained firing in spinal motor neurons (MNs) when studied in reduced animal preparations. The most prevalent type of PIC in spinal MNs is that mediated by L-type voltage-gated Ca^{2+} channels found in dendrites. Several ideas have been proposed as to the functional significance of PICs, both in terms of the control of normal motor function and as an impaired process contributing to various neurological disorders. Yet the extent to which PICs contribute to natural MN activity is not known. To address this gap, we recorded activity in the same triceps surae motor units before and after pharmacological inhibition of PICs while trained rats performed a ramp-and-hold isometric plantar flexion task. Extensive effort was expended to ensure rats remained calm and

self-motivated while performing the task. Motor unit activity was recorded with intramuscular microelectrode arrays. PICs were inhibited by delivering a fast-acting L-type calcium channel antagonist (nimodipine, 10 - 30 μg) to the lumbar spinal cord through an implanted intrathecal catheter. In five animals tested thus far, no significant change ($p = 0.52$) was observed in motor unit firing rates following nimodipine injection (mean ± SD, pre-nimodipine: 20.5 ± 6.2 Hz, post-nimodipine: 22.2 ± 7.4 Hz). The most straightforward interpretation of these preliminary findings is that PICs play little role during normal voluntary contractions under low stress conditions.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.10/EE6

Topic: F.09. Motor Neurons and Muscle

Support: Craig H. Neilsen SCIRTS Award
Alvin and Marion Birnschein Foundation Grant
Marquette University Regular Research Grant and Summer Faculty Fellowship

Title: Optical H-reflex analysis for assessment of motor and sensory axon opsin expression during optogenetic peripheral nerve stimulation

Authors: E. MORAVEC[1], L. W. READ[1], ***J. WILLIAMS**[1,2];
[1]Joint Dept. of Biomed. Engin., Marquette Univ. and the Med. Col. of Wisconsin, Milwaukee, WI; [2]Dept. of Neurosurg., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Optogenetic peripheral nerve stimulation is emerging as a promising neuromodulation therapy for restoring movement after neurological injury. Optical stimulation of mixed sensory-motor nerves may recruit both motor and sensory neurons depending on opsin expression patterns. In animals with opsin expression in both populations, the extent to which sensory neurons contribute to optically evoked muscle activity remains unclear. Because motor and sensory pathways generate muscle activity through distinct mechanisms, methods to assess functional sensory neuron opsin expression are important for development of optogenetic rehabilitation therapies. One potential approach is to analyze the monosynaptic stretch reflex, or H-reflex, during optical nerve stimulation.
In this study, we examined the feasibility of optically activating the H-reflex circuit and its utility for evaluating opsin expression in motor and sensory axons. We first performed optogenetic tibial nerve stimulation in a transgenic mouse model with robust peripheral motor and sensory neuron opsin expression while recording electromyography (EMG) activity from the lateral gastrocnemius. Muscle responses exhibited characteristics consistent with both direct motor

activation and sensory-mediated H-reflex activity, including multiphasic responses and frequency-dependent depression of the later H-wave component. Transection of the sciatic nerve proximal to the stimulation site eliminated the H-wave, providing additional evidence of reflex pathway activation.
We then applied a similar methodology in rats receiving intramuscular AAV injections with vectors of varying sensory and motor neuron tropism (e.g., AAV6, AAV-PHP.S). H-waves were observed in rats exhibiting histological sensory neuron transduction and demonstrated both rate-dependent depression and elimination following proximal sciatic nerve lidocaine block.
These results demonstrate the utility of optical H-reflex analysis for assessing the functional contribution of sensory axon opsin expression to optically evoked muscle activity. This approach may be particularly useful for evaluating novel viral vectors with unknown tropism or cell-type specificity, screening vectors for motor- or sensory-specific expression, and may provide a general tool for investigating cell-type-specific contributions to sensorimotor reflex circuits.

Disclosures: E. Moravec: None. **L.W. Read:** None. **J. Williams:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR319.11/EE7

Topic: F.09. Motor Neurons and Muscle

Support: AHA Grant 25CDA1445873

Title: Motor Unit Firing Dynamics Underlying the Inhibitory Nature of Cervical Vestibular Evoked Myogenic Potential

Authors: *C. CUADRA[1], I. NOVOA CORNEJO[2], E. MARTINEZ-VALDES[3];
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Abstract: Vestibular-evoked myogenic potentials (VEMPs) are used to assess vestibulospinal function, where brief tone bursts generate inhibitory and excitatory short- and medium-latency responses in the sternocleidomastoid (SCM). Although these responses have been examined at the single motor-unit level, the mechanisms underlying cVEMP generation remain incompletely understood at the motor-unit population level. Prior intramuscular studies sampled few units and could not determine whether vestibulospinal inhibition is uniformly distributed across the active motor pool. We addressed this gap by combining high-density surface electromyography decomposition with peri-stimulus time histogram (PSTH) and peri-stimulus frequencygram (PSF) analyses to characterize cVEMP inhibition at the motor-unit population level. Five healthy adults maintained tonic SCM activation during 500-Hz, 120-dB SPL acoustic stimulation. Thirteen tracked SCM motor units were analyzed using cumulative-sum methods to estimate inhibition onset, duration, amplitude, and integrated strength. PSTH-derived inhibition onset

averaged 11.2±5.9 ms, whereas PSF analysis captured a later, sustained inhibitory phase. The combined PSTH+PSF analysis estimated the full inhibitory epoch to be 39.9±10.1 ms. Vestibular stimulation produced near-complete, uniform suppression across tracked units, despite substantial inter-participant variability in the strength of integrated inhibition. These findings suggest that cVEMP amplitude variability may reflect differences in the temporal common inhibitory drive across motor units rather than differential inhibition of individual units. This approach provides a mechanistic framework for interpreting vestibulospinal inhibition from surface EMG measurements and may be extended to other muscles targeted by descending vestibulospinal signals.

Disclosures: C. Cuadra: None. **I. Novoa Cornejo:** None. **E. Martinez-Valdes:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR319.12/EE8

Topic: F.09. Motor Neurons and Muscle

Support: Project EBRAINS-Italy (IR00011) from the Italian Ministry of University and Research

Title: Spatio-temporal dynamics of cortical excitability modulation during action observation: a TMS-EEG study

Authors: *A. MANCUSO[1], M. BAZZINI[2], R. ROSSI[2], A. NUARA[1], G. HASSAN[3], L. FERRARI[4], G. FURREGONI[3], M. FABBRI-DESTRO[2], S. CASAROTTO[3], M. ROSANOVA[3], P. AVANZINI[2];
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Abstract: Since the first evidence of the mirror mechanism (MM) in humans, Transcranial Magnetic Stimulation (TMS) has emerged as a key tool for probing modulation of corticospinal excitability during action observation (AO). However, conventional TMS approaches mainly capture changes within the primary motor cortex, providing only a partial account of how such modulation unfolds across the sensorimotor system. A more comprehensive understanding of the spatiotemporal fingerprint of cortical dynamics can be achieved by combining TMS with Electroencephalography (TMS-EEG), allowing direct tracking of TMS-evoked responses across the whole scalp with high temporal resolution. To address this aim, we stimulated the left dorsal premotor cortex - a node of MM - in a sample of 18 volunteers, while 64-channel EEG was continuously recorded. TMS pulses were delivered while subjects observed reach-to-grasp actions, landscapes, or a black screen. Individual MRI-guided neuronavigation and real-time TMS-evoked potentials (TEPs) monitoring were used to optimize stimulation parameters and

minimize magnetic and muscular artifacts. We first focused on local changes in cortical excitability by analyzing the amplitude of TEPs over electrodes closest to the stimulation site: we observed a significant amplitude reduction during AO compared to the other conditions across early (~50 ms), middle (~100 ms), and late (~250 ms) latency ranges. We then examined whether this local modulation extended to broader cortical activities. A topographic analysis of variance revealed significant condition-dependent differences in scalp distribution temporally overlapping with the local amplitude effects. The TEPs recorded during AO exhibited topographic patterns that deviated from those observed during control conditions and a higher natural frequency, i.e., the dominant TMS-induced oscillatory activity within the first hundred milliseconds after the TMS pulse. These changes in TMS-evoked responses indicate that AO shapes the spatiotemporal dynamics of cortical activity, modulating response amplitude, topographical organization, and intrinsic oscillatory properties. Moreover, they support TMS-EEG as a powerful approach to characterize how action-related information is dynamically routed within the human motor system, beyond corticospinal output alone. Combining stimulation of multiple sites with whole-scalp recordings may help to reconstruct the causal timing and directionality of premotor, parietal, and motor contributions to AO, providing a network-level account of the MM in humans.

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Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.13/EE9

Topic: F.09. Motor Neurons and Muscle

Title: Correlating excitability and brain hemodynamics using a multimodal TMS-EEG-EMG-fNIRS

Authors: *K. MAHMAT, E. KALLIONIEMI;
Dept. of Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ

Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation method that activates neurons, increasing cortical and corticospinal excitability as measured by electroencephalography (EEG) and electromyography (EMG), respectively. TMS targeting the motor cortex can be used to treat a variety of neurological disorders. However, TMS-evoked responses are highly variable across subjects due to poorly understood sources, thereby reducing the efficiency of TMS treatment. Neural and hemodynamic responses in the brain are tightly coupled, a relationship known as the neurovascular mechanism. Understanding how hemodynamic responses predict TMS-evoked excitability may therefore help elucidate between-subject variability. Although existing evidence shows a link between excitability and

hemodynamic responses using different modalities, none have examined how baseline excitability and brain hemodynamics are related using a multimodal TMS-EEG-EMG-fNIRS framework within the same cortical region. Therefore, the main goal of this study is to investigate the association between TMS-evoked excitability and task-related brain hemodynamics in the left primary motor cortex. 23 right-handed healthy adults (25.69 ± 4.46 years old; 7 females) were recruited for the following experiments. 1) 100 single pulse TMS pulses at 90%rMT to find the **cortical excitability,** quantified by beta synchronization across several peak latencies, 2) recruitment curve protocol to derive the **corticospinal excitability**, and 3) finger-tapping and breath-holding tasks to quantify **brain hemodynamics** for all hemoglobin concentrations. The brain hemodynamics evoked by finger-tapping positively predicted corticospinal excitability, with a positive link between slope of the recruitment curve and Peak-HbO ($p<0.0001$, $r^2=0.55$), Peak-HbT ($p<0.0001$, $r^2=0.57$), AUC-HbR ($p=0.007$, $r^2=0.31$), Std-HbO ($p<0.0001$, $r^2=0.61$), Std-HbR ($p=0.002$, $r^2=0.38$), as well as Std-HbT ($p<0.0001$, $r^2=0.59$). Breath-holding-related brain hemodynamics negatively predicted brain synchronization, with inverse links between AUC-HbO and beta-P30 ($p=0.041$, $r^2=0.22$), beta-P45 ($p=0.008$, $r^2=0.34$), beta-P60 ($p=0.011$, $r^2=0.32$), beta-N100 ($p=0.019$, $r^2=0.28$). These results may suggest that hemodynamic responses of the human cortex should be considered when designing TMS protocols in both experimental and clinical settings.

Disclosures: K. Mahmat: None. **E. Kallioniemi:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant P41EB018783
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Title: Operant Conditioning of Cutaneous Reflexes in the Arm: Methods Development and Initial Data

Authors: *M. L. MCKINNON[1], J. ROSS[1], J. A. BRANGACCIO[2], J. R. WOLPAW[2]; [1]BioCircuit Technologies, ATLANTA, GA; [2]Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr. & State Univ. of NY, Albany, NY

Abstract: Operant conditioning of reflexes is a powerful therapeutic strategy for enhancing recovery of function after CNS injury (for review: doi:10.3389/fnint.2014.00025). Most work to date has focused on conditioning the H-reflex (an electrical analog of the largely monosynaptic spinal stretch reflex). Recent work has shown promise in operant conditioning polysynaptic

cutaneous reflexes (CRs) in the lower limb. Preliminary results suggest a correlation between CR up-conditioning and reduction of chronic pain in the conditioned limb. In an effort to expand this possible therapy to pain that affects the arm, we here describe our initial efforts to develop CR conditioning protocols for the upper limb. We have focused to date on optimization of reflex elicitation.
In 5 healthy adults, a pair of bipolar stimulating hydrogel electrodes were placed over the ulnar nerve, either at the wrist or over the fifth digit. Recording electrodes were placed over the abductor digiti minimi (ADM) and the flexor carpi ulnaris (FCU) muscles in each person. An isolated stimulator delivered a train of 15 biphasic square pulses (1ms total pulse width, 2ms pulse interval). Pulse intensity was increased gradually to identify the subject's sensory, radiating, and discomfort thresholds. A sequence of 20 pulse trains at a 5s interstimulus interval (ISI) was delivered at both stimulation locations in each person. Evoked responses were recorded in both target muscles. To ensure that the observed responses were spinally mediated CRs rather than direct muscle responses we evoked M-waves and F-waves by increasing the stimulation intensity during wrist stimulation. To ensure the observed responses were not voluntary withdrawal from stimulation, we reduced stimulus intensity to a barely perceptible level and asked the person to contract the FCU when the stimulus was perceived.
We observed upper limb CRs in every person. The optimal protocol varied across people. Some showed stronger responses to finger stimulation, others to wrist stimulation. Some had stronger responses in the ADM, others in the FCU. In every person, the evoked reflex latencies were greater than the M-wave and F-wave latencies, and less than the latency of the voluntary contraction upon stimulus perception. These data begin to establish a basis for developing CR operant conditioning reflex protocols for the upper limb. Next steps include trying to modify CRs by operant conditioning and examining the impact of this conditioning on the person's sensory, radiating, and discomfort thresholds.

Disclosures: M.L. McKinnon: A. Employment/Salary (full or part-time):; BioCircuit Technologies. **J. Ross:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. **J.A. Brangaccio:** None. **J.R. Wolpaw:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

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Program #/Poster #: PSTR319.15/EE11

Topic: F.09. Motor Neurons and Muscle

Support: EBrains-Italy

Title: Tango ergo moveo. The role of somatosensory perception in fine motor skills learning ability through AOT: an EEG study.

Authors: *A. GIORGI[1], M. DEL VECCHIO[3], M. FABBRI-DESTRO[4], A. ERRANTE[2], L. FOGASSI[1], P. AVANZINI[5];

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Abstract: Action Observation Training (AOT) promotes motor skill acquisition, yet the mechanisms underlying its effects and the biomarkers tracking AOT-based motor learning remain poorly understood. Fine motor skills critically depend on the integration of somatosensory feedback and motor commands, particularly during manipulative actions relying on haptic processing. Intracranial studies using Somatosensory Evoked Potentials (SEPs) identified the N140 component as reflecting sustained activity in posterior opercular regions involved in action execution and observation. Here, we investigated whether SEP dynamics, and particularly the N140, track motor learning induced by AOT. Forty right-handed participants (20 AOT, 20 controls; mean age=26.0±2.4 years) completed three training sessions across one week. On each training day, participants performed four repetitions of a clay manipulation task. In the AOT group, each execution trial was preceded by the observation of an expert performing the task on video, whereas control participants viewed a static image. SEPs elicited by right median nerve stimulation (1000 trials, ISI randomized 1-2 s) were recorded before and after each session. SEP data were analyzed using mass-univariate cluster-based permutation testing to identify training-related changes across sessions and days. EEG measures were then correlated with behavioral learning outcomes. Performance improved across trials and days in all participants (all $p<0.001$). Although no main group effect emerged, AOT participants outperformed controls on Day 3 ($p=0.028$). Both groups showed a significant post-training increase in contralateral N140 amplitude (120-200 ms). However, longitudinal SEP changes differed between groups: in the AOT group, they were predominantly expressed over ipsilateral parietal regions, whereas in controls, they remained largely confined to the contralateral parietal spot and were accompanied by additional later activity (~280-330 ms). Importantly, progressive increases in ipsilateral N140 amplitude across training days were associated with greater behavioral improvement, exclusively in the AOT group. These findings suggest that manipulative motor learning is accompanied by changes in higher-order somatosensory processing. Distinct hemispheric modulation patterns in AOT and control participants may reflect different neural mechanisms supporting skill acquisition. The association between N140 modulation and behavioral improvement further suggests that the N140 component may represent a neurophysiological marker of learning-related plasticity during AOT-based fine motor learning.

Disclosures: A. Giorgi: None. **M. Del Vecchio:** None. **A. Errante:** None. **L. Fogassi:** None. **P. Avanzini:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR319.16/EE12

Topic: F.09. Motor Neurons and Muscle

Support: FAPESP Grant 2025/01398-5

Title: Motor overflow facilitates handgrip force recovery while scalp electroacupuncture modulates corticospinal excitability in healthy adults

Authors: *K. ZHANG[1], S. N. BORIN[1], F. D. BONI[2], G. BATTAGLION[1], J. E. DE ARAUJO[3]; [1]Hlth. Sci., [2]Univ. of São Paulo, Ribeirão Preto, Brazil; [3]Hlth. Sci., Univ. of São Paulo, Ribeirao Preto, Brazil

Abstract: Motor overflow is characterized by involuntary activation of homologous muscles during high-intensity unilateral contractions and has been associated with increased corticospinal excitability. Scalp acupuncture has also been reported to modulate motor cortical activity, but its interaction with motor overflow remains unclear. We investigated the effects of motor overflow and scalp electroacupuncture on handgrip force recovery and corticospinal excitability in healthy adults.One hundred fifty-four right-handed healthy participants (18-59 years) were randomly allocated into five groups: Control (n=30), Scalp Acupuncture (SA, n=31), Overflow (OF, n=31), Sham Scalp Acupuncture plus Overflow (SSA-OF, n=31), and Scalp Acupuncture plus Overflow (SA-OF, n=31). Participants performed a handgrip fatigue protocol consisting of three maximal contractions. Overflow was induced by simultaneous maximal isometric flexion of the contralateral index finger. Scalp electroacupuncture was delivered over the left primary motor area (2/15 Hz, 20 min). Handgrip force was analyzed using linear mixed models and a recovery index (T3-BL3). A neurophysiological subgroup (n=68) underwent transcranial magnetic stimulation to assess motor evoked potential (MEP) latency, amplitude, and duration.All groups exhibited a decline in force during baseline trials, confirming fatigue induction. Recovery index analysis revealed significant group differences ($F = 7.266$, $p < 0.0001$). The OF group demonstrated greater recovery (14.26%) than the Control (-2.15%; $p<0.0001$) and SA (3.32%; $p=0.0069$) groups. SSA-OF (9.59%) and SA-OF (10.34%) also showed greater recovery than Control ($p<0.01$), with no differences relative to OF. MEP latency showed significant side-dependent interactions, but no global intervention effects. MEP amplitude demonstrated significant condition effects ($p=0.0003$), whereas MEP duration exhibited significant effects of group ($p=0.036$), condition ($p<0.0001$), group × condition interaction ($p=0.036$), and group × side × condition interaction ($p=0.0051$).Motor overflow effectively attenuated fatigue-related force decline and represented the primary functional facilitator. Scalp electroacupuncture did not enhance or suppress the behavioral effects of overflow but produced measurable changes in corticospinal excitability. These findings suggest that neurophysiological adaptations may precede detectable functional gains and support further investigation of repeated neuromodulatory interventions in neurological populations.

Disclosures: K. Zhang: None. **S.N. Borin:** None. **F.D. Boni:** None. **G. Battaglion:** None. **J.E. De Araujo:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR319.17/EE13

Topic: F.09. Motor Neurons and Muscle

Support: 2025/23027-9

Title: Motor Overflow Preserves Handgrip Force Following Fatigue in Healthy Women

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Abstract: Background: Motor overflow is the involuntary facilitation of motor output in muscles contralateral to an active contraction. Previous studies have shown that overflow can acutely enhance handgrip strength; however, it remains unknown whether this facilitatory effect persists after fatigue has been established.Objective: Determine whether motor overflow preserves handgrip force after the onset of muscular fatigue.Methods: Ninety-nine healthy women participated in this study and were allocated to four groups: Control Right (CD, n=25), Control Left (CE, n=23), Overflow Right (OD, n=26), and Overflow Left (OE, n=25). Participants performed repeated maximal handgrip contractions until force decreased by at least 30% relative to the initial contraction, then completed three additional contractions. In the test condition, participants in the overflow groups executed a contralateral motor task to induce motor overflow, whereas control groups repeated the same protocol without intervention. Because the onset of fatigue varied among participants, data were aligned to the fatigue event. The first contraction reaching the fatigue criterion was defined as F0, followed by three post-fatigue contractions (F1-F3). The mean force across F0-F3 was calculated for both the baseline and test conditions. The primary outcome was the difference between test and baseline post-fatigue force (ΔMean). Group differences were analyzed using one-way ANOVA followed by Tukey-Kramer post hoc tests.Results: A significant effect of group was observed for ΔMean ($F(3,95)=10.90$, $p<0.0001$). Overflow groups demonstrated greater preservation of force following fatigue (OD=12.66±1.61%; OE=10.90±1.64%) than control groups (CD=2.30±1.64%; CE=2.61±1.71%). Post hoc analyses revealed significant differences between both overflow groups and both control groups (all $p\leq0.0039$). No differences were observed between OD and OE ($p=0.8699$) or between CD and CE ($p=0.9992$), indicating that the effect was independent of the side used to induce overflow.Conclusions: Motor overflow significantly preserved handgrip force after fatigue had been established. This effect occurred regardless of the side used to induce overflow, indicating that motor overflow remains effective under fatigued conditions. These findings support motor overflow as a robust phenomenon that sustains force production following fatigue.

Disclosures: G.G.S. Battaglion: None. **S.N. Borin:** None. **K. Zhang:** None. **J.E. De Araujo:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Topic: F.09. Motor Neurons and Muscle

Support: FAPESP Grant 2025/01398-5 and 2026/03469-0
CAPES Finance Code 001

Title: Unilateral Auricular Stimulation Attenuates Motor Overflow-Induced Facilitation in Healthy Adults

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Abstract: Motor overflow is the involuntary facilitation of remote muscles during voluntary contractions and may reflect increased motor network excitability. Auricular stimulation is a promising neuromodulatory approach, particularly in the cavum conchae, which is predominantly innervated by the auricular branch of the vagus nerve. Although vagal auricular stimulation has been associated with central nervous system effects, its influence on motor overflow remains unknown. We investigated whether unilateral auricular stimulation modulates overflow-induced facilitation of handgrip strength in healthy adults.A total of 173 healthy young participants were allocated to one of six experimental conditions: Control, Overflow, mechanical stimulation of the scaphoid fossa, mechanical stimulation of the cavum conchae, active photobiomodulation applied to the scaphoid fossa, and sham photobiomodulation consisting of mechanical contact without light emission applied to the same region. All auricular interventions were delivered exclusively to the right ear. Overflow was induced using a previously validated protocol involving sustained contractions of non-homologous muscles. Handgrip strength was measured before and after the intervention, and percentage changes from baseline were calculated.Overflow significantly increased handgrip strength compared with Control (3.99% vs. -2.07%; $p=0.0256$), confirming the protocol's facilitatory effect. In contrast, all auricular stimulation conditions reduced this overflow-induced facilitation. Significant differences were observed between Overflow and scaphoid fossa mechanical stimulation ($p<0.0001$), cavum conchae stimulation ($p<0.0001$), active 660-nm photobiomodulation ($p=0.0003$), and sham photobiomodulation ($p<0.0001$). No significant differences were detected among the auricular stimulation conditions. Furthermore, the behavioral effects were observed bilaterally, and no Group × Side interaction was detected.These findings demonstrate that unilateral auricular stimulation attenuates motor overflow-induced facilitation in healthy adults. The absence of differences among stimulation modalities suggests that activation of sensory afferents from multiple auricular territories may be sufficient to influence the neural processes underlying motor overflow. The bilateral effects observed following unilateral stimulation are consistent with, although do not establish, the involvement of central neuromodulatory mechanisms. Motor overflow may provide a sensitive behavioral model for investigating the effects of auricular neuromodulation on human motor function.

Disclosures: J.E. De Araujo: None. **K. Portes:** None. **K. Zhang:** None.

Poster

PSTR319: Motor Neurons: Activity, Identification, and Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR319.19/EE15

Topic: F.09. Motor Neurons and Muscle

Support: Saitama Prefecture Association of Physiotherapists Research Grant
Japan Science Association Sasagawa Grant Foundation Research Grant

Title: Analysis of Neuromuscular Recruitment and Lower Limb Coordination During Gait Maturation in Toddlers

Authors: *C. YAMASAKI[1], M. ITO[2], T. KOKUBUN[3];
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Abstract: Independent walking is achieved through the maturation of locomotor control and postural stability during infancy. Mature gait consists of coordinated joint movements and phasic muscle activity, whereas early gait is characterized by restricted joint motion and unstable neuromuscular control. Previous studies have mainly focused on central nervous system development; however, developmental changes in peripheral neuromuscular control during gait maturation remain unclear. We analyzed longitudinal changes in motor unit (MU) recruitment and lower limb coordination during gait maturation in toddlers.Five toddlers and five healthy adults participated in this study. Surface electromyography and three-dimensional motion analysis were synchronized to record neuromuscular activity and kinematic data during gait. Target muscles were the rectus femoris (RF), biceps femoris (BF), tibialis anterior, and lateral gastrocnemius. Range of motion (ROM) and coefficient of variation (CV) of lower limb joint angles were calculated during gait. Inter-joint coordination variability was evaluated using normalized deviation (ND) derived from hip-knee angle-angle plots. In addition, regression coefficients (RC) between MU action potential amplitude and firing frequency were calculated to evaluate MU recruitment characteristics during gait maturation.Results showed that during the stance phase, hip and knee ROM remained lower in toddlers compared with adults, whereas CV gradually increased with walking experience. ND also remained higher during stance even after increased walking experience. MU analysis demonstrated muscle-specific maturation patterns. RF showed progressive changes in RC toward adult-like values with increasing walking experience, whereas BF exhibited relatively adult-like recruitment patterns from earlier developmental stages.The increase in coordination variability together with changes in MU recruitment suggests that gait maturation is characterized not simply by reduction of movement variability, but by expansion of flexible neuromuscular control strategies. During stance, toddlers may gradually increase lower limb degrees of freedom while simultaneously modulating postural support through broader MU recruitment. Thus, peripheral neuromuscular adaptations may contribute to the maturation of stable locomotion during early gait development.

Disclosures: C. Yamasaki: None. **M. Ito:** None. **T. Kokubun:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.01/EE16

Topic: G.01. Neuroethology

Support: HHMI

Title: The neural basis of cuttlefish camouflage and social behavior

Authors: *T. MONTAGUE[1,2], T. BARLOW[1], E. SHOOK[1], C. J. GIBBONS[1], Y. XU[1], D. GARCIA-ROSALES[1], J. J. FEATHER[3], E. P. SIMONCELLI[4], L. ABBOTT[1], R. AXEL[1]; [1]Columbia Univ., New York, NY; [2]Howard Hughes Med. Inst., New York, NY; [3]Carnegie Mellon Univ., Pittsburgh, PA; [4]Neural Sci., New York Univ., New York, NY

Abstract: All animals form internal neural representations of the external world that guide their behavior. Cuttlefish, coleoid cephalopods related to octopus and squid, perform visually driven adaptive camouflage by dynamically altering the color, pattern, and texture of their skin to create an approximation of their surroundings - a process directly controlled by the brain. Thus, cuttlefish perform a remarkable sensorimotor transformation: they recreate what they see on their skin, generating a motor output that approximates the sensory input itself. In addition to camouflage, cuttlefish use their dynamic skin to communicate with conspecifics using a series of innate skin patterns that reveal the animal's internal state. We are using the cuttlefish skin behaviors to understand how the physical properties of the visual world are represented by patterns of neural activity in the brain, and how this representation is transformed into an approximation of the physical world on the skin. We have performed a series of experiments to develop the dwarf cuttlefish, *Ascarosepion bandense*, as a model to investigate the neural basis of camouflage and social communication. We have sequenced the genome, developed gene editing techniques, completed a 3D brain atlas, developed camouflage and social behavior paradigms, examined dwarf cuttlefish behavior in the wild, and adapted miniscopes for underwater imaging. Furthermore, we recently succeeded in generating transgenic cuttlefish that express genetically-encoded calcium indicators in the brain, permitting the live imaging of neural activity. We are now using these technologies to simultaneously record neural activity and measure behavior to uncover how visual information is deconstructed in the brain, and then reconstructed into an image of the physical world on the skin.

Disclosures: T. Montague: None. **T. Barlow:** None. **E. Shook:** None. **D. Garcia-Rosales:** None. **J.J. Feather:** None. **E.P. Simoncelli:** None. **L. Abbott:** None. **R. Axel:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.02/EE17

Topic: G.01. Neuroethology

Support: TUBITAK Grant 120E198

Title: Selective Closed-Loop Manipulation of Active Sensing Movements in Weakly Electric Fish

Authors: *E. AYDIN[1], I. UYANIK[2];
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Abstract: Weakly electric fish actively shape the sensory signals they receive by moving within their environment. During refuge tracking, these movements include both task-related pursuit and higher-frequency, off-target components that may serve active sensing. Because perception and action are coupled in closed loop, manipulating self-generated sensory consequences is essential for testing whether these movements are functional rather than incidental motor variability. We developed a fish-in-the-loop paradigm to selectively modify active sensing feedback during refuge tracking in freely swimming adult *Eigenmannia virescens* (n=5) and *Apteronotus albifrons* (n=5). Fish tracked a sinusoidally moving refuge at 0.10, 0.15, and 0.25 Hz. Their position was measured real time and reinjected into refuge motion with feedback gain γ. We compared an unfiltered condition, in which the complete movement signal was reinjected, with a structure-aware FIR-filtered condition that suppressed narrowband target-tracking components while preserving off-target, active-sensing-weighted motion. Selective filtering produced sign-dependent behavioral effects. Under negative feedback (γ=-1), filtered feedback consistently improved pursuit: target response and gain increased, normalized tracking error and off-target/target motion decreased, and the fraction of motion power concentrated at the target frequency increased. In contrast, positive feedback (γ=0.5) increased movement variability and reduced target concentration, indicating amplification of self-generated sensing dynamics. These effects were reproducible across stimulus frequencies. Our results show that active sensing movements are not merely additive motor noise. Instead, they participate in a closed-loop sensorimotor process whose behavioral consequences depend on how self-generated motion is fed back to the animal. Frequency-selective manipulation provides a causal framework for dissociating pursuit from active sensing in freely behaving animals.

Disclosures: E. Aydin: None. **I. Uyanik:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.03/EE18

Topic: G.01. Neuroethology

Title: Recovering active sensing objectives in weakly electric fish using inverse reinforcement learning

Authors: ***E. RUTBIL**[1], O. KARAGOZ[3,4], M. M. ANKARALI[3,4], I. UYANIK[1,2];
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[3]Electrical and Electronics Engin., [4]Ctr. for Robotics and AI, Middle East Tech. Univ., Ankara, Turkey

Abstract: Active sensing is a biological mechanism that enables animals to shape their sensory input by making purposeful movements to improve perception, especially in uncertain environments. In weakly electric fish, these movements are oscillatory swimming motions that enhance the quality of sensory feedback from their self-generated electric fields. Prior work modeled these movements as control signals that minimize predictive uncertainty in state estimation, using a predefined cost function with weights. While the framework successfully reproduces observed behavior, its cost structure was assumed a priori rather than inferred directly from behavior.

In this study, we use inverse reinforcement learning (IRL) to infer the implicit cost function governing active sensing directly from behavior, rather than assuming its structure as prior work did. An IRL framework based on feature expectation matching is implemented, and Particle Swarm Optimization is used to estimate weights from simulated expert trajectories. First, we validate the approach by demonstrating that the learning algorithm can reliably recover the true weights used in the prior active sensing model. We then extend the feature set beyond previously assumed terms by including additional uncertainty-related terms and longer-horizon features. To address identifiability issues arising from correlated features, sparsity-inducing regularization is introduced.

The results show that the proposed framework can identify dominant features while suppressing redundant terms and can recover a cost function that successfully reproduces the tracking behavior of the fish. These findings provide insight into the structure of biological active sensing strategies and establish IRL as an approach for uncovering sensing objectives from behavior.

Disclosures: E. Rutbil: None. **O. Karagoz:** None. **M.M. Ankarali:** None. **I. Uyanik:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

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Program #/Poster #: PSTR320.04/EE19

Topic: G.01. Neuroethology

Support: DOD NDSEG Fellowship
NIH 1R01NS140174

Title: Active sensing movements for tuning self- and externally- generated mechanosensory signals in Drosophila

Authors: *T. MCCABE, M. P. SUVER;
Vanderbilt Univ., Nashville, TN

Abstract: Animals have evolved special sensory systems to detect changing external conditions and respond by moving through space. For flying insects like the fruit fly *Drosophila melanogaster*, successful flight requires the ability to sense both exteroceptive (external) stimuli like wind and proprioceptive (self) stimuli like wingbeats to adequately navigate. The fruit fly antennae contain a large mechanosensory organ called the Johnston Organ, innervated by thousands of Johnston Organ Neurons (JONs) subsets of which function as proprioceptors and exteroceptors. These mechanosensors are dynamically positioned by antennal muscles during flight, changing the mechanosensory information detected. We aim to understand how this kind of active sensing flexibly alters antennal mechanosensation for specific behavioral states. Using *in vivo* calcium imaging, we quantify how active movement shapes mechanosensory activity. These experiments have revealed optimal positions that increase the gain of both proprioceptive and exteroceptive stimuli. Further, these studies point towards corollary discharge mechanisms that could allow antennal mechanosensors to differentiate between proprioceptive and exteroceptive stimulation. Overall, this work serves as an example of how active sensing strategies can use less sensors to detect and differentiate multiple signals at once, thereby reducing the number of sensors necessary for a comprehensive representation of the environment.

Disclosures: T. McCabe: None. **M.P. Suver:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR320.05/EE20

Topic: G.01. Neuroethology

Support: 2R15GM125073-03
NSF IOS 2042873

Title: Mushroom Body-Associated Pathways Integrate Metabolic and Gustatory Cues to Guide Oviposition

Authors: *D. SITARAMAN[1], Y. LEE[3], K. WISE[2];
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Abstract: Female *Drosophila melanogaster* encounter sugar as both a nutritive cue and an oviposition cue, yet the same stimulus can drive distinct behavioral outcomes depending on context. While sucrose is attractive in feeding, mated females often avoid sugar-containing substrates during egg laying, indicating that shared sweet-taste inputs are routed differently across behavioral states. Previous work from our laboratory showed that flies require both the

taste and nutritive value of sugar to guide oviposition decisions, suggesting that metabolic signaling contributes to how substrate value is evaluated. Insulin signaling has been implicated in taste processing and internal-state-dependent behavior, but its role in oviposition choice and the higher-order neural pathways through which it acts remain unresolved. We hypothesize that insulin signaling modulates oviposition site selection through **mushroom body-associated pathways** that integrate sweet-taste input, nutritional state, and reproductive context. In this model, sweet-sensing gustatory pathways provide shared sensory information to the subesophageal zone, where taste signals are relayed through higher-order taste projection neurons and distributed to brain regions involved in behavioral selection. Mushroom body-associated circuits are well positioned to mediate this transformation because they receive convergent sensory and modulatory input and can bias behavioral output according to context. Within these pathways, Kenyon cell-associated circuits, mushroom body output neurons, and modulatory partners may act together to assign oviposition-specific meaning to sugar cues. Insulin receptor function may therefore influence how sweet-taste information is interpreted within mushroom body-associated oviposition circuits. Rather than acting solely at the level of peripheral taste detection, insulin signaling may regulate the gain, salience, or downstream routing of sweet input as it enters higher-order circuits. Disruption of insulin signaling in specific mushroom body-associated pathways is predicted to shift oviposition preference, potentially reducing the ability of mated females to avoid sugar-containing substrates during egg laying. Together, these studies will define how insulin signaling interacts with mushroom body-associated pathways to guide taste-dependent oviposition decisions. More broadly, this work will help reveal how shared sensory inputs are transformed into distinct behavioral outputs, providing insight into the neural mechanisms that link internal metabolic state, sensory evaluation, and reproductive action selection in *Drosophila*.

Disclosures: D. Sitaraman: None. **Y. Lee:** None. **K. wise:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.06/EE21

Topic: G.01. Neuroethology

Title: Prey immobilization by the venom of Heteropteran predators Belostoma testaceum and Limnoporus canaliculatus

Authors: *C. C. SWART;
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Abstract: Recent work has revealed a rich cocktail of neuroactive chemicals present in several representative semi-aquatic Heteropteran predators. There is significant diversity in this group (Nepomorpha) of over 2000 species in 11 families and venom of only 3 species have been investigated. Current data indicate significant diversity in venom components within the group as

well as in comparison to their close relatives the terrestrial Heteroptera (Pentatomidae and Reduviidae). Given the potential value these compounds may have for basic neuroscience research further investigation of venom action within the group is warranted. Herein, I present data on prey immobilization time, pattern of prey muscle EMG response and cholinergic activity of venom from species of Belostomatidae (*Belostoma testaceum*) and Gerridae (*Limnoporus canaliculatus*). Imobilization times for belostomatid bugs when attacking aquatic amphipods varies depending on capture orientation and injection site but averages 32 seconds from attack to immobility. EMG recording of muscle while insect venom was injected indicated significant effects of Belostomatid venom on muscle tone in both cholinergic gastropod muscle and Glutamatergic insect muscle (*Periplaneta sp*.) Venom of the Gerrid species, *L. canaliculatus* did not elicit any paralytic effects on either type of muscle. When introduced to the Ellman assay for Cholinesterase activity, neither venom showed the ability to alter rate of acetylthiocholine catabolism directly. Belostomatid venom likely acts at the level of the motor neuron rather than the neuromuscular junction.

Disclosures: C.C. Swart: None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

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Program #/Poster #: PSTR320.07/EE22

Topic: G.01. Neuroethology

Support: NIH R01 NS118562
NSF 2525492
NIH R01 NS143970

Title: Modeling signal propagation in visual projection neurons

Authors: *O. S. WADHWA[1], B. HINA[2], A. MORENO-SANCHEZ[1], C. R. VON REYN[2,1], J. AUSBORN[1];
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Abstract: How animals process visual features is an open question in neuroscience. We use the escape pathway in Drosophila melanogaster to investigate this fundamental question. Flies detect looming stimuli, such as approaching predators on a collision course, and initiate escape responses. Loom detection is in large parts mediated by a class of visual projection neurons called lobula plate lobula columnar type II (LPLC2) neurons. These LPLC2 neurons receive graded, non-spiking information from upstream direction-selective T4/T5 neurons. They then integrate this information and pass it down to spiking descending neurons that give rise to a motor command. Recent electrophysiological data from our labs have suggested that LPLC2 neurons produce action potentials superimposed on a large, graded depolarization in response to

looms. Additionally, the receptive fields of these neurons, when measured using the underlying graded depolarization, are larger than those measured using action potentials alone. This raises the question of what information reaches the axon terminals to influence downstream neurons: only action potentials, or both action potentials and graded depolarizations? Electrophysiological recordings from these neurons are obtained from the soma, which is electrotonically distant from the rest of the neuron. Because the spike initiation zone and axon terminals are electrophysiologically inaccessible, we built connectome-constrained, morphologically detailed single-neuron biophysical models to predict information transfer to the terminals. We also used machine learning tools to perform data-driven inference of biophysical parameters in our models. Our simulations predict that action potentials propagate reliably to the axon terminals, while graded potentials attenuate significantly. Additionally, we identified similar biophysical parameter regimes across multiple LPLC2 morphologies, suggesting that these conclusions are robust to morphological variation.

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Poster

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Topic: G.01. Neuroethology

Support: NEI 1F31EY037197-01
NINDS R01NS118562
NSF-IOS 2525492

Title: Characterizing visual feature encoding in Drosophila Visual Projection Neurons LPLC1 and LPLC2

Authors: *B. W. HINA[1], H. CROKE[1], A. MORENO-SANCHEZ[2], O. S. WADHWA[2], N. SMOLIN[1], J. AUSBORN[2], C. R. VON REYN[1,2];
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Abstract: An animal's visual system quickly and reliably detects salient features from its environment to guide appropriate behavioral responses. However, restricted access to visual circuits has limited our understanding of how and where visual features are encoded in the brain. We leverage the *Drosophila melanogaster* visual system due to its wide array of genetic tools and accessible and well mapped visual circuits. We investigate visual projection neurons (VPNs), visual cell types that retinotopically tile the visual field and transmit visual information from the optic lobes to the central brain. Controversies persist regarding which visual features VPNs encode, whether they are narrowly or broadly tuned, and how they convey visual

information. We focus on two VPN cell types LPLC1 and LPLC2. Previous studies have suggested they are non-spiking neurons, with debates on whether they selectively encode objects approaching on a direct collision course, or broadly respond to additional visual features, such as translating objects. Using whole-cell electrophysiology, we find LPLC1 and LPLC2 are spiking neurons that respond robustly to looming stimuli that simulate approaching objects. Consistent with this observation, both cell types exhibit high densities of the voltage gated sodium channel para in their axons, indicating spike initiation zones. Using single-cell recordings of LPLC2 and electron microscopy-derived estimates of receptive field location, we demonstrate that only a small subset of the population responds to a given looming stimulus. We also find LPLC1 and LPLC2 spike to translating stimuli, and that the size of their receptive fields, based on spiking responses, are smaller than those reported with Ca^{2+} imaging. Tuning for LPLC1 and LPLC2 show notable differences in responses to distinct size and speeds across loom and translation stimuli. Our work reveals VPNs spike to encode visual information and uncovers key differences in feature encoding between two similar cell-types. These findings may help uncover fundamental mechanisms for feature encoding within more complex organisms.

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Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.09/EE24

Topic: G.01. Neuroethology

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National Institutes of Health NINDS R01NS118562 (J.A. and C.R.v.R.)

Title: Visual feature detection and motor transformation in a Drosophila collision avoidance network

Authors: *H. CROKE[1], B. W. HINA[2], J. AUSBORN[3], C. R. VON REYN[2,3];
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Abstract: A central question in neuroscience is how the brain transforms sensory information into motor action. Despite its importance, our understanding of sensorimotor computation remains limited by the lack of accessible circuits with known connectivity. Recent electron microscopy volumes of the *Drosophila melanogaster* brain and ventral nerve cord (VNC, analogous to the vertebrate spinal cord) now provide synapse-level wiring diagrams of the entire nervous system. Leveraging these connectomes alongside genetic tools, behavioral assays, and electrophysiology, we aim to understand how the brain detects visual threats and converts that information into appropriate motor action. When a fly detects an object approaching on a

collision course, it executes an evasive saccade - a stereotyped, high-speed turn away from the visual threat. This behavior is robust, repeatable, and linked to specific visual features, making it an ideal model for studying sensorimotor transformations. Using the connectome, we identified a hierarchical network of interconnected descending neurons (DNs) - neurons that carry information from the central brain to the VNC to drive motor output - that are well positioned to drive collision avoidance saccades. We identified one DN, DNp03, as a hub for collision avoidance in flying flies. DNp03 receives visual information related to looming objects and connects to motor neurons of the wings and neck, enabling the coordinated movements of an evasive saccade. Optogenetic activation of DNp03 reliably evokes saccades, yet silencing DNp03 only partially disrupts looming responses. These data suggest additional hub DNs exist within the saccade network, that function in parallel with DNp03. We identified two, DNp26 and DNp57, where silencing disrupts, but does not eliminate the turning response to loom, similar to DNp03. All three DNs receive excitatory visual input from LPLC4, a population of retinotopically organized neurons situated four synapses downstream of photoreceptors. LPLC4 are well poised to play a central role in detecting looming stimuli during flight, but to date remain functionally uncharacterized, leaving open questions regarding the specific visual features they encode. We address this through whole-cell electrophysiology in behaving flies, and find LPLC4 respond to motion and luminance changes presented within their receptive field. This approach provides a unique platform to dissect how visual signals are processed and transformed across multiple layers - from feature detection in the optic lobe to descending neuron networks in the central brain.

Disclosures: H. Croke: None. **B.W. Hina:** None. **J. Ausborn:** None. **C.R. von Reyn:** None.

Poster

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Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.10/EE25

Topic: G.01. Neuroethology

Support: Animal Behavior Society Student Research Grant 103661

Title: Neurobiological factors affecting mass swimming behavior in larval zebrafish: sensory and mental states

Authors: *W. J. BOTTA[1], B. MISTRY[2], N. ANAGNOSTOU[2], S. GARNIER[2], K. E. SEVERI[3]; [1]Biol., [2]New Jersey Inst. of Technol., Newark, NJ; [3]Federated Dept. of Biol. Sci., New Jersey Inst. of Technol. (NJIT), Newark, NJ

Abstract: Mass behavior is the rapid adoption of similar behavior by individuals within a group. It is a common strategy for behavioral coordination in many species such as schooling fish and flocking birds, but can also lead to negative outcomes through unregulated spread of behavior. Mass behavior is influenced by various factors including sensory information processing and

mental states. Previous studies have focused on a single individual or a small group, suggesting that increased detection of conspecifics and their behavior through sensory means increases the likelihood of behavioral adoption by an individual, with this likelihood being further influenced by the observed conspecifics' mental states. However, we sought to analyze social group dynamics on a larger scale using larval zebrafish, a model that allows for pharmacological and transgenic accessibility. Larval zebrafish have been found to exhibit a spontaneous mass-swimming behavior at high group densities where many individuals in a group will rapidly swim in the same direction at the same time. We tested the effects of sensory input by manipulating visibility via environmental light level, and the lateral line, via ablation, in zebrafish larvae and observing the impact on their mass-swimming behavior when in dense groups. Likewise, we tested effects of different pharmaceutically-induced mental states on this mass swimming behavior while in dense groups by bath-applying the anxiogenic caffeine and the anxiolytic fluoxetine. Larvae were recorded with high-speed video in custom arenas for 10 minutes and exposed to constant light or darkness. Contrary to the prediction that improved perception of conspecifics should allow for increased adoption of behavior, the dark environment was associated with more frequent mass-swimming events, not less. However, lateral line-ablated larvae showed a drastic reduction in mass-swimming in both light and darkness. Additionally, caffeine surprisingly reduced the occurrence of mass swimming behavior, while fluoxetine did not have a strong effect. These results suggest a more complex interplay between these different sensory systems and the adoption of behavior, wherein some senses are required for the behavior to occur while others modulate its intensity.

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Poster

PSTR320: Neuroethology: Sensory Motor Systems

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Program #/Poster #: PSTR320.11/EE26

Topic: E.07. Visual Sensory-Motor Processing

Support: IOS-1855956
IOS-2338596

Title: Stimuli strength reconfigures decision-state dynamics in the zebrafish isthmotectal circuit

Authors: *L. GALLART, L.-W. KONG, A. BIZYAEVA, A. HEIN;
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Abstract: Decision making in the animal world often appears to be organized around two-alternative choices. Although this may seem like a highly reductionist strategy for processing complex environments, evidence from zebrafish and other animals suggests that selection among multiple distributed targets is achieved by chaining together multiple two-alternative decisions.

The processing of multiple threats by zebrafish, and the choice of which threat to flee from, may similarly involve reducing the problem to a two-alternative choice, with occasional compromise responses in which the animal escapes along a trajectory that avoids both stimuli. This computation has been proposed to rely on the isthmotectal circuit described by Fernandes et al., 2021. Across species, the nucleus isthmi has emerged as an important modulatory component of sensorimotor behavior, contributing to focal enhancement of sensory responses in the optic tectum of barn owls and sustained target pursuit in zebrafish.Here, we develop a mathematical model of the isthmotectal biological circuit and show that its topology is sufficient to generate a rich repertoire of dynamics. These dynamics depend not only on the asymmetry between perceived threats, but also on the overall strength of sensory input. At low input strength, the model exhibits a single point attractor, which may prevent responses to irrelevant stimuli. As input strength increases, the system transitions into regimes with two- and three-point attractors, allowing rapid responses to stimulus asymmetry while maintaining robustness to noise. Across a wide range of parameters, the circuit also exhibits history-dependent responses, such that prior stimulus exposure can shape subsequent choice states. Finally, at higher overall input strength, the system returns to a single-attractor regime, suggesting that an additional circuit may be required to compute compromise escape trajectories that avoid both stimuli. To test these predictions, we are using a close-loop VR set up on freely moving adult zebrafish. Fish are chased by two differently sized dots that appear perpendicular to their velocity and through trials change the overall size of the dots. All Together, we leverage published connectivity and behavioral findings to build a dynamical model of the circuit, which in turn proposes falsifiable predictions for new experiments. Our findings show that a biologically grounded circuit with simple topology can generate flexible decision-state dynamics, providing a solid step toward understanding how the brain produces behavior that is both fast and robust.

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Poster

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HFSP RGP0045/2022
Simons Foundation SFI-AN-NC-SCN-00007276-05
ONR N00014-23-1-2086

Title: Superior colliculus responses during flight and echolocation of Egyptian fruit bat

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Abstract: The superior colliculus (SC) is a midbrain structure responsible for multisensory integration and rapid action planning. However, traditional SC research has primarily relied on highly controlled, head-fixed experiments, and recent naturalistic experiments focus on a single sensory modality, such as vision in rodents or audition in bats. Consequently, how the SC dynamically coordinates sensory fusion during unrestrained exploration remains poorly understood. To address this gap, we investigated SC responses in freely moving Egyptian fruit bats (*Rousettus aegyptiacus*). This species is an excellent model for our work, given its strong reliance on both vision and tongue-click echolocation, as well as its ability to flexibly switch between and integrate these two systems. To record the bats' SC activity and monitor natural behavior, we leveraged wireless electrophysiology alongside microphone, gyroscopic, and accelerometer recordings. Additionally, bats were released into an anechoic chamber equipped with an array of 32 microphones and 5 high-speed cameras to reconstruct sonar beam direction and flight path. In this paradigm, bats were allowed to search for a perch to land and rest as a reward. Preliminary data show that putative superficial SC neurons fire strongly during flight and navigation before landing. We find that these firing rates are modulated by both click timing and body movements, and logistic regression of binned firing rates can reliably predict flight activity. To probe the effects of visual input to SC during flight, we also compare neural and behavioral recordings in white and red light conditions. Since bats are insensitive to longer wavelengths, the red light condition acts as a low vision environment. In red light, we find that the bats produce increased clicks, corresponding to higher SC activity and increased latency to landing. These results demonstrate that the SC drives key navigational behaviors, including flight dynamics and active sensing in a highly visual and auditory animal, and that altering visual cues can modify these active sensing behaviors. In the future, this work will provide a foundation to study how the SC integrates multisensory information with internal states, as bats decide whether to explore an area or land on a perch.

Disclosures: C. Rasgaitis: None. **D. Drieskens:** None. **A. Krishna:** None. **M. Jaroszewski:** None. **J. Sayles:** None. **C.F. Moss:** None.

Poster

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Topic: G.01. Neuroethology

Support: NIH R01 DC022604-02
MathWorks Fellowship
Quad Fellowship
American Australian Association Graduate Education Scholarship

Title: A neural circuit for millisecond-scale, single-neuron credit assignment in a songbird

Authors: *J. M. WHITE[1], J. R. SCHERRER[2], A. N. PLUMP[3], M. S. FEE[4];
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Abstract: Learning from experience requires identifying which actions, at which times, lead to a particular outcome. This problem of credit assignment is fundamental to both biological and artificial learners. Songbird vocal learning presents a particularly demanding credit assignment problem: singing is controlled by millisecond-precise activity of thousands of motor neurons, but song quality is encoded by a diffuse, delayed dopamine signal with more than an order of magnitude less temporal precision. It is unknown how precisely the songbird brain can drive changes in specific premotor neurons at specific times to improve song performance. To answer this question, we developed a closed-loop neurofeedback system (neuron-conditional auditory feedback, nCAF) that allows us to impose correlations between auditory feedback and the activity of individual premotor neurons at specific times in song. We find that playing disruptive auditory feedback (DAF) contingent on the activity of a targeted neuron in the vocal variability-generating premotor nucleus LMAN (lateral magnocellular nucleus of the anterior nidopallium) at one time in song causes adaptive changes in the activity of the targeted neuron with 3.3 ± 0.4 ms temporal precision (mean ± s.d., n=15 units in 3 birds). Uncorrelated neighboring neurons do not learn, representing single-cell spatial precision. In addition, we find that learning only occurs when auditory feedback follows contingent activity with a delay less than 126 ms (95% CI = 108 to 140 ms, n=48 units in 3 birds), suggesting that the learning circuit is finely tuned to plausible physiological feedback latencies. These findings challenge the prevailing view of dopamine-mediated reinforcement as slow and imprecise, and expand our understanding of the limits of credit assignment in the brain.

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Poster

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.14/EE29

Topic: G.01. Neuroethology

Title: Mesoscale Cortical State Dynamics During Active Place Avoidance: A Widefield Calcium Imaging State-Space Approach

Authors: *K. SAXENA[1], M. LEHMAN[1], I. OLADEPO[3], J. HOPE[2], P.-H. CHENG[2], T. BECKERLE[2], S. B. KODANDARAMAIAH[4];
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Abstract: Spatial avoidance learning simultaneously recruits multiple brain regions. Traditionally, studies have focused on understanding the role played by individual brain regions in mediating spatial avoidance. How multiple disparate brain regions coordinate their activity during avoidance behavior is as yet unclear. We use a miniaturized headmounted microscope to image a wide field of view of the dorsal cortex during an Active Place Avoidance (APA) task. In the Active Place Avoidance (APA) task, mice are positioned on a rotating circular arena and must learn to avoid a stationary, wedge-shaped "shock zone." Entry into this specific area results in a penalty via electrical foot stimulation. The experimental protocol consisted of ten 10-minute sessions, conducted as five sessions per day. Through repeated exposure and feedback from these penalties, mice learn to interpret spatial cues to determine the shock zone's location. Widefield GCaMP imaging data from 10 animals across 40 sessions were analyzed. Imaged brain data were Z-scored to produce dF/F signals from 27 common Allen Brain Atlas cortical regions for each animal. All data were then dimensionally reduced using k-means clustering, where all frames of dF/F activity were assigned to one of K frames summarizing most common spatial expressions. At K = 6 frames, the model was able to reconstruct the original brain data with 80% accuracy. These 6 summary frames identified unique patterns of spatial activity during several common APA behaviors. During chaining (defined as the animal being passively transported to the shock zone), mice exhibited somatosensory-dominant cortical activity (~43% of frames), whereas shock events (electrical foot stimulation) recruited motor areas. In early APA sessions, mice exhibited posterior cortical activity prior to avoidance; by late sessions, these same events were preceded by lateral somatosensory activity. These results demonstrate the utility of widefield calcium imaging for revealing learning-related cortical reorganization during avoidance behavior.

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Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR320.15/EE30

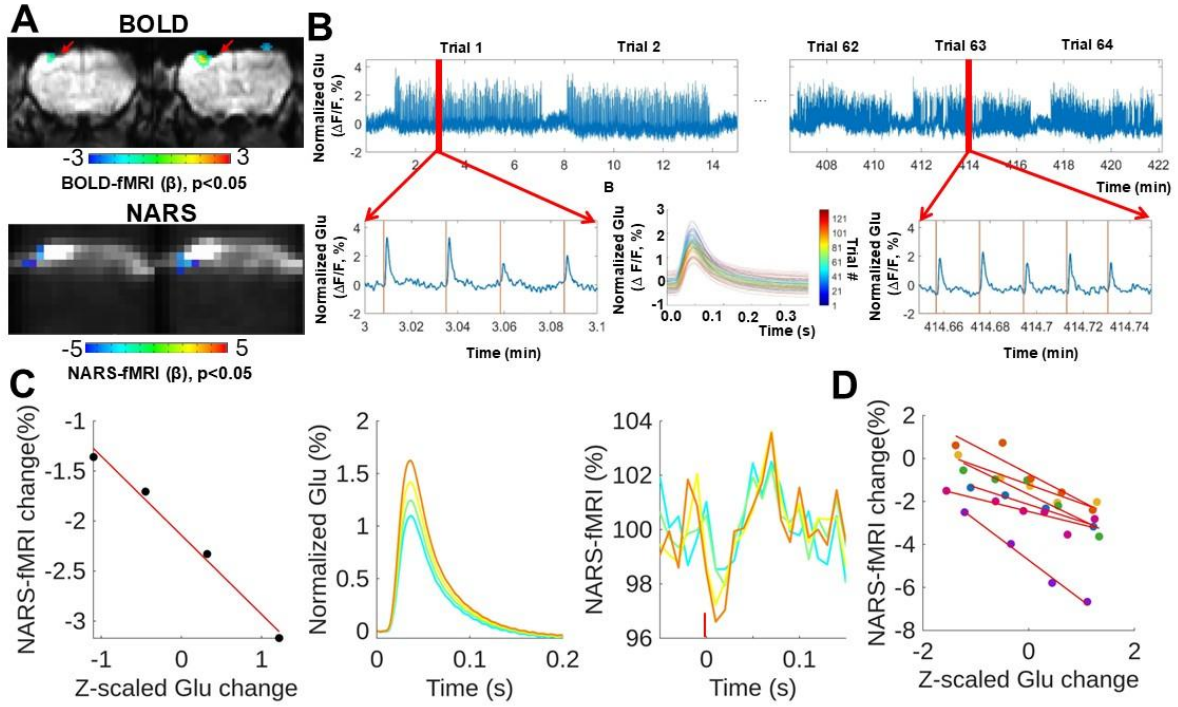
Topic: G.01. Neuroethology

Support: RF1NS124778
R01NS122904
S10MH124744
S10OD03621

Title: Neuronal-activity-related sodium (NARS) fMRI reveals fast brain dynamics beyond hemodynamic contrast

Authors: *X. YU[1], X. LIU[2], G. YU[2], Y. JIANG[2], N. PASUPATHY[2], D. HIKE[2], X. A. ZHOU[2]; [2]Athinoula A. Martinos Ctr. for Biomed. Imaging, [1]Massachusetts Gen. Hosp., Boston, MA

Abstract: Brain-wide, noninvasive methods that directly resolve neuronal activity on millisecond timescales are still lacking in neuroimaging. Hemodynamic fMRI (^{1}H-based) provides whole-brain maps of activity, yet its vascular origin creates spatial and temporal displacements from neuronal events that complicate interpretation, especially in disease conditions where neurovascular coupling is altered. Here, we developed an ultrafast ^{23}Na fMRI platform at 14 T that combines a reshuffled k-t 3D gradient echo readout (TR/TE, 10ms/1ms) with an implantable RF coil and respiration-gated acquisition. This configuration provides the sampling rate and SNR needed to probe quadrupolar T2*-weighted single quantum sodium dynamics on the neuronal timescale. Across rats and mice, somatosensory forepaw stimulation produced a localized ^{23}Na signal decrease of ~2-3% in the FP-S1, peaking ~10-30 ms post-stimulus. The activity pattern is well matched with conventional BOLD-fMRI maps acquired in the same animals. Trial-by-trial measurements during simultaneous iGluSnFR glutamate fiber photometry demonstrated that larger evoked glutamate transients coincided with larger NARS decreases, supporting a neuronal origin of the NARS contrast. We interpret the negative NARS response as a transient activity-dependent redistribution of sodium ions toward restricted, protein-rich microdomains, where more restricted rotational dynamics may accelerate T2*short decay and produce a 2-3% signal decrease without requiring large changes in bulk sodium concentration. Together, these results establish neural activity-related sodium (NARS) fMRI as a viable approach for direct, mesoscale neuronal mapping with MRI at millisecond resolution.



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Liu: None. **G. Yu:** None. **Y. Jiang:** None. **N. Pasupathy:** None. **D. Hike:** None. **X.A. Zhou:** None.

Poster

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Topic: G.01. Neuroethology

Support: KAKEN 26KJ0878

Title: Go-response of stop or licking shapes task learning and behavioral separation of visual go/no-go task in head-fixed mice

Authors: *S. NISHIMOTO[1,2,3], M. WATANABE[4], A. FUNAMIZU[2,3];
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Abstract: Go/no-go discrimination tasks using visual stimuli in head-fixed mice are widely used to study cognitive and perceptual decisions, yet how the go-response action shapes learning and behavior has not been systematically examined. We trained male C57BL/6J mice on a self-initiated visual go/no-go task in which a high-luminance visual stimulus was rewarded with water upon a go response, whereas a low-luminance stimulus required withholding the response. We prepared two different go responses while keeping the overall trial schedule unchanged. In one task, mice were required to lick a spout to receive a reward (lick group, n = 12). In the other, mice had to decelerate their running speed below a predefined threshold. (stop group, n = 10). During initial training in which reward was automatically delivered with the visual stimuli irrespective of behavior, the licking and running speeds were anticorrelated across mice. The stop group required more number of training sessions compared to the lick group ($p = 0.048$, Mann–Whitney U-test), with the excess confined to Go-only acquisition stages; the number of sessions required after No-Go trials were introduced did not differ ($p = 0.36$). At criterion performance, the lick group showed stimulus discrimination through licking behavior (lick count and reaction time within 0-0.95 s after target onset), whereas the stop group did not. Nevertheless, the stop group exhibited earlier divergence between Go and No-Go running speeds (divergence time, $p = 0.021$, Mann-Whitney U-test) and lower within-session performance variability ($p = 0.044$). Ridge logistic-regression decoding of trial type from binned licking and speed features in the second preceding the decision window exceeded label-shuffled controls in both groups (lick: $p = 4.9e-4$; stop: $p = 2.0e-3$, Wilcoxon signed rank test) with no significant difference in accuracy between groups; running speed at 0.75-0.95 s after displayed target onset carried the largest decoder weight in both groups. Bias-corrected mutual information about stimulus type was comparable across groups, but minimum-MI partial information decomposition uncovered divergent structure: unique stimulus information in running speed was higher in the stop group ($p = 0.032$, Mann–Whitney U-test), whereas the synergistic fraction of

the joint lick-speed code was larger in the lick group ($p = 0.019$). Go-response modality thus reorganizes learning demands, behavioral readouts, and the partitioning of stimulus information across co-measured variables, with direct implications for the design and interpretation of mechanistic neural studies in head-fixed perceptual decision paradigms.

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Poster

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Topic: G.01. Neuroethology

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R15NS135396

Title: Brain-wide organization of proximity to criticality predicts engagement in spontaneous behavior

Authors: A. FONTENELE[1], ***W. L. SHEW**[2];
[1]Physics Dept., Univ. of Arkansas Fayetteville, Fayetteville, AR; [2]Univ. of Arkansas, Fayetteville, AR

Abstract: Brain-wide neural circuits generate actions depending on the cues the animal receives from the world. For decades, neuroscience has scrutinized how actions are encoded during repetitive tasks when behavior is instructed by controlled sensory cues, but in the real world, animals exhibit rich behavior even in more open-ended scenarios without clear cues. How is such uninstructed behavior generated and which brain areas are involved? We hypothesized that this challenge - intrinsic generation of rich dynamics, without external cues - is well-suited to a neural system that operates near criticality, a marginally stable state with emergent multi-scale dynamics. We studied multi-area Neuropixels recordings in mice, measuring each area's proximity to criticality using d_2, an information theoretic metric based on temporal renormalization group theory. We confirmed our hypothesis and discovered an organization principle: each brain area's proximity to criticality strongly predicts its correlation with spontaneous behavior. This organization is specific to uninstructed behaviors; it is abolished during a constrained visuomotor task. Our results suggest that the intrinsic source of rich, unconstrained behavior comprises a widespread constellation of brain areas operating near criticality.

Disclosures: A. Fontenele: None. **W.L. Shew:** None.

Poster

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Program #/Poster #: PSTR320.18/FF1

Topic: G.01. Neuroethology

Support: National Science and Technology Innovation 2030-Major Project 2021ZD0203303

Title: Neural mechanisms underlying yawning and its role in arousal promotion

Authors: *K. CHEN, W. ZHANG;
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Abstract: Organisms experience recurrent activities adhered to homeostatic regulation, such as sleep-wake and reproductive cycle. How will animals react when external environment forbids them to perform highly motivated behaviors? Previous studies have reported that yawning is highly correlated with drowsiness, penile erection —states that correspond to sleep debt and sexual drive. Therefore, we focused yawning, a conserved behavior observed across vertebrates, suggesting a phylogenetic origin and essential functions. But the systemic neural mechanisms underlying the initiation and physiological significance of yawning remain poorly understood. Here, we established a wake-yawn paradigm to induce yawning in *Mus musculus,* which efficiently induced 2.43 (±1.81) yawns in 40 minutes. Secondly, we performed electrocardiogram recording showing that heart rate increased during yawning (before yawn: mean 588.14 beats/minute, during yawn: mean 608.54 beats/minute). Fiberphotometry revealed that locus coeruleus (LC) neurons expressing dopamine beta-hydroxylase (DBH) were activated during yawning. Interestingly, we also found that LC DBH^+ neurons activated during both mouth opening and closing in anesthetized mice whose mouths are gaped manually. As length of masseter changes during mouth gaping, we next focused on trigeminal mesencephalic nucleus (Me5) sensing masseter stretching via PIEZO2 channel. Besides, it's reported that Me5 projects to LC. We then knocked out PIEZO2 expression in Me5 and found that activity of LC DBH^+ neurons didn't change significantly during yawning ($p=0.1356$, $n=17$). So yawn-associated LC activation is mediated by proprioception from masseter. Notably, Me5 PIEZO2 knockout significantly increased yawning frequency ($p<0.001$, $n=14$). Finally, we performed optogenetic activation of paraventricular nucleus of hypothalamus (PVN) oxytocinergic neurons and observed that mice yawned during 10-minute laser on period (mean=3.857, SD=2.143, n=14). To conclude, we developed a behavioral paradigm to induce yawning in mice, which paves way for future studies on yawning in mice. And yawning promotes arousal through masseter-Me5-LC axis. Besides, PVN Oxytocinergic neurons are sufficient to trigger yawning. Our research suggests that vertebrates produce yawn to quench drowsiness during the transition state between wake and sleep. Given that proproception from masseter mediates yawning-induced arousal, self-awareness might help animals to suppress drives such as sleepiness and sexual drive while sleep and mating is not available.

Disclosures: K. Chen: None. **W. Zhang:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

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Program #/Poster #: PSTR320.19/FF2

Topic: G.01. Neuroethology

Support: Howard Hughes Medical Institute

Title: Polis: An Integrated Hardware and Software Suite for Studying Rat Societies

Authors: Y. PAN[1], D. SCHAUDER[2], B. J. ARTHUR[3], J. ARNOLD[4], M. LALIT[2], ***D. G. TERVO**[2];
[1]Janelia research campus, [2]Janelia Res. Campus, Ashburn, VA; [3]Scientific Computing, Howard Hughes Med. Inst., Ashburn, VA; [4]HHMI, Ashburn, VA.

Abstract: Social animals live in complex societies, continuously adapting their behavior to the behavior of others, giving rise to emergent group-level properties that in turn influence the individual's behaviors and physiology. Understanding these bidirectional relationships requires capturing events across a range of timescales — individual behaviors over hundreds of milliseconds and society-level dynamics over a span of weeks. Here we present Polis, a platform combining video, vocalization recording, and wireless electrophysiology to enable uninterrupted examination of behavior and neural activity in rat societies across this range. Polis achieves multimodal acquisition and control using Robot Operating System (ROS), synchronizes data streams from ROS nodes using Precision Time Protocol (PTP) in a single coherent system, allowing for microsecond and millisecond alignment across modalities. A key advantage of Polis is that it enables the acquisition of episodic wireless recording of neural activity for weeks from multiple rats simultaneously. We have successfully implemented Polis in "Rat City," where we record from the prefrontal cortex in multiple rats simultaneously. Recordings yielded stable populations of well-isolated single units over days. These results establish Polis as a platform for studying how population neural activity supports social behavior in naturalistic settings.

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Poster

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NIH Grant 5R34NS138066-02

Title: Coordinated Neural Circuits for Infant-Parent Thermal Homeostasis

Authors: *B. ITO[1], R. C. FROEMKE[2];
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Abstract: Effective parental care requires continuous monitoring of offspring state and rapid behavioral adjustments to ensure survival. In altricial species like mice and humans, infants cannot thermoregulate independently and rely on caregivers for thermoregulatory support. Thus, survival depends on an infant's ability to sense and communicate thermal needs to caregivers, and on the caregiver's ability to interpret and act on these cues. Here, I identify a temperature-dependent feedback loop between maternal care and pup signaling that links offspring physiological state to maternal caregiving behavior. I designed a thermal arena to test how mothers integrate environmental and offspring cues to guide pup retrieval. Mothers rapidly mapped the thermal landscape and retrieved pups to the warmest location in the environment. When presented with pups of different temperatures, mothers retrieved the coldest pups first, indicating that maternal retrieval decisions are guided by offspring thermal state. In turn, pups placed on cool surfaces emitted ultrasonic vocalizations within seconds, preceding drops in core temperature, suggesting that these calls signal early changes in thermal state to trigger caregiver responses. Together, these findings suggest a bidirectional communication system in which infants broadcast need in real-time and caregivers translate these cues into corrective actions. By linking thermosensation to decision-making in parental care, this work reframes infant thermoregulation as a coordinated homeostatic process between parents and offspring, providing a framework for studying how sensorimotor circuits transform infant physiological state into caregiving actions.

Disclosures: B. Ito: None. **R.C. Froemke:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.21/FF4

Topic: G.01. Neuroethology

Title: Immediate and Persistent Impairments in Social Behavior and Hippocampal CA1 Ultrastructure Following Chronic Toluene Inhalation in Adolescent Rats

Authors: *N. POCHKHIDZE;
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Abstract: Chronic inhalation of the organic solvent toluene during adolescence alters hippocampal microarchitecture and social behavior. Adolescent male rats (PND 25-30) were exposed to toluene inhalation (2000 ppm) for 40 days. Social interactions were quantified 24 hours post-exposure to evaluate acute neurotoxicity, and reassessed following a 90-day abstinence period to determine long-term behavioral outcomes. To correlate structural and behavioral changes, transmission electron microscopy (TEM) was performed at both time points (24 hours and 90 days post-exposure), targeting asymmetric synapses within the hippocampal CA1 stratum radiatum. Morphometric analysis quantified synaptic density, postsynaptic density (PSD) thickness, presynaptic vesicle pool distribution, and mitochondrial ultrastructure.Toluene inhalation induced an immediate suppression of social behaviors during the acute phase, which failed to recover and persisted as a permanent deficit after 90 days of abstinence. TEM morphometry revealed a severe reduction in total synaptic density within the CA1 region at both time points. This synaptic loss was accompanied by a depleted pool of presynaptic vesicles—specifically within the readily releasable pool—and a significant thinning of the PSD. Additionally, pre- and postsynaptic compartments showed distinct mitochondrial pathology, including severe swelling and disrupted cristae, which remained evident after the prolonged abstinence.Chronic adolescent toluene exposure causes immediate neurotoxic structural damage that persists into late adulthood. The concurrent depletion of functional vesicle pools, thinning of the PSD, and localized mitochondrial degradation within the CA1 network provide a clear ultrastructural substrate for the long-term socio-cognitive deficits observed following prolonged abstinence.**Funding Support:** This work was supported by the Shota Rustaveli National Science Foundation of Georgia (SRNSFG) [Grant Number YS-24-194].

Disclosures: N. Pochkhidze: None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.22/FF5

Topic: G.01. Neuroethology

Support: NSF Award DBI 2050311

Title: Vasoactive intestinal polypeptide involvement in mouse communication and social behavior

Authors: *C. E. WATERS[1], D. FERREIRA[2], L. HURLEY[1];
[1]Dept. of Biol., Indiana Univ., Bloomington, IN; [2]Univ. of Illinois Chicago, Chicago, IL

Abstract: Vasoactive intestinal polypeptide (VIP) has been shown to modulate multiple aspects of social behavior in birds, but not much is known about its role in communication or social behavior in mammals. Female house mice (*Mus musculus*) utilize a suite of behaviors during courtship interactions to signal rejection or to pace an interaction with a male, one of which is the production of broadband vocalizations (BBVs, or "squeaks"). Males are sensitive to these signals, showing suppressed production of ultrasonic vocalizations (USVs) and increased activity in auditory nuclei like the inferior colliculus (IC) in response to squeak playback. However, the specific circuitry and cell types in the IC involved in responses to female squeaks are relatively unknown. A potential target is a subpopulation of VIP-producing glutamatergic cells because of their stellate morphology and distribution across frequency laminae, indicating that VIP cells may be involved in processing broadband sounds. To this end, we performed several experiments to investigate how VIP cells in the IC respond to female squeak playback and the effects of systemic VIP injections on social behaviors in adult male CBA/J mice. Tagging of VIP and FOS mRNA in the IC of males using fluorescence *in situ* hybridization following playback of female squeaks showed an increase in overall FOS production compared to silence. However, squeak playback decreased the number of VIP and FOS double-labeled cells, suggesting that activity in VIP cells was suppressed while non-VIP activity in the IC increased. Following intraperitoneal injection of VIP, males in both opposite-sex and same-sex interactions produced fewer vocalizations and spent less time investigating the stimulus mouse, indicating reduced social motivation in response to increased global VIP. The suppression of VIP-producing cells in the IC in response to social vocalizations in conjunction with social deficits following a systemic increase in VIP implicate VIP as a potential key modulator in the integration of both sensory and social systems for appropriate communication between conspecifics.

Disclosures: C.E. Waters: None. **D. Ferreira:** None. **L. Hurley:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.23/FF6

Topic: G.01. Neuroethology

Support: NIH Grant DC02853
NIH Grant NS140062
NSF Grant IOS-2154646
CNPq/MCTI/FNDCT Grant 22/2024
CAPERS Fellowship

Title: Analysis of the auditory representation of vocalizations in a pallial cortical circuit

Authors: T. A. VELHO[1], R. B. COSTA[2], ***C. V. MELLO**[3];
[1]Brain Inst., Brain Inst. / Federal Univ. of Rio Grande do Norte, natal, Brazil; [2]Brain Inst., UFRN - Federal Univ. of Rio Grande do Norte, Natal, Brazil; [3]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The caudomedial nidopallium (NCM), a high-order auditory cortical area of songbirds, is involved in the perceptual processing and memorization of conspecific vocalizations, but many aspects of its organization and function remain incompletely understood. Our recent work using molecular markers and immediate-early genes to map neuronal activation uncovered evidence of the complexity of NCM's organization and selective responses to conspecific vocalizations compared to other complex auditory stimuli. Here we analyze these questions in further detail. Assessments of *in situ* hybridization patterns from the ZEBrA (Zebra finch Expression Brain Atlas; www.zebrafinchatlas.org) database revealed dozens of transcripts with differential expression across rostral vs. caudal NCM, some with sharp expression gradients. Some rostral markers had distinct dorsal-ventral patterns, including low expression in dorsal and ventral domains relative to central NCM. Together with differential expression compared to the more rostrally positioned Field L2a, these patterns helped delineate rostral, dorsal, and ventral NCM. Expansion of the quantitative assessment of regional differences through densitometry helped refine these NCM domain definitions. Bioinformatics and gene ontology (GO) assessments of the differential markers provided insights into molecular pathways and functions that may be differentially enriched across NCM sub-regions. By comparing the expression of the activity-inducible immediate-early gene *zenk* in response to conspecific and heterospecific vocalizations and non-vocal auditory stimuli we obtained evidence of consistently higher responses in dorsal NCM and higher selectivity of caudal NCM toward conspecific song. Comparing *zenk* induction in inhibitory vs. excitatory cells provided evidence of strong activation of the inhibitory network of rostral NCM by non-conspecific stimuli, in particular heterospecific song. We also found that the spatial organization of responsive cells is highly sensitive to both spectral and temporal components of song. Using catFISH mapping, enhanced by linear discriminant analysis of the spatial distribution of the responses, we obtained evidence of broadly distributed song-selective neuronal ensembles and that individual NCM neurons participate in the representation of different conspecific songs. We present possible schemes that may explain these differential activation patterns, taking into account the limited data on regional connectivity. This study sheds light onto the functional organization and perceptual processing roles of NCM in the context of songbird vocal communication.

Disclosures: T.A. Velho: None. **R.B. Costa:** None. **C.V. Mello:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

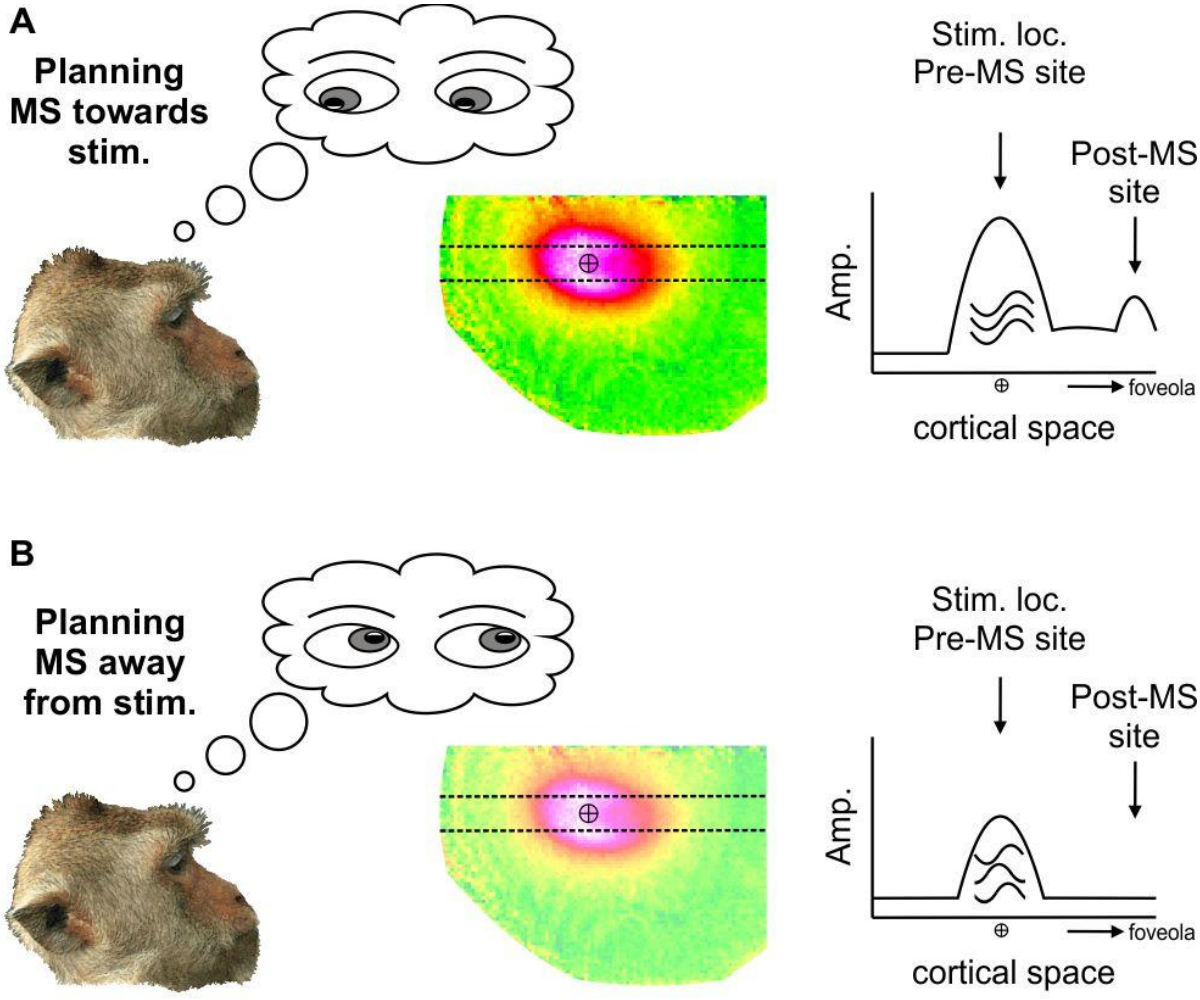
Program #/Poster #: PSTR320.24/FF7

Topic: E.07. Visual Sensory-Motor Processing

Title: Premicrosaccadic neural enhancement of the current and future stimulus location in foveal V1

Authors: T. BOUHNIK[1], O. KORCH[1], ***H. SLOVIN**[2];
[1]The Gonda Multidisciplinary Brain Res. Center, Bar-Ilan Univ., Ramat Gan, Israel; [2]The Gonda Multidisciplinary Brain Res. Ctr., Ramat Gan, Israel

Abstract: Microsaccades are miniature saccades performed during visual fixation that were shown to play a pivotal role in active sensing. Recent studies suggested that pre-microsaccade attention may underlie the enhanced visual processing at the stimulus site. However, the neuronal mechanism underlying this phenomenon at the foveal scale remains unknown. Using voltage-sensitive dye imaging, we investigated the neural responses to uninstructed, spontaneous microsaccades in the fovea of the primary visual cortex (V1) in monkeys. We found that before a microsaccade onset toward a stimulus, the neuronal activity at the current and future landing stimulus sites was enhanced. This enhancement was spatially confined to the current and future landing stimulus sites, which appeared to merge along the microsaccade trajectory in V1. Finally, we found that a pre-microsaccade increased synchronization at the current stimulus site. Our findings shed new light on the neural modulations preceding microsaccades and suggest a link to neural signatures of attention.



Disclosures: T. Bouhnik: None. **O. Korch:** None. **H. Slovin:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR320.25/FF8

Topic: G.01. Neuroethology

Support: NIH Grant K99EY037495
NIH Grant R21MH134183
Yale Kavli Institute for Neuroscience Postdoctoral Award for Collaborative Excellence

Title: Prelimbic norepinephrine modulates threat representation and behavior in a novel height threat task

Authors: *S. M. STASZKO[1], E. KRISHNAMURTHY[1], R. LOKANADHAM[2], A. BASU[3], A. P. KAYE[1];
[1]Dept. of Psychiatry, [2]Yale Univ., New Haven, CT; [3]Psychiatry, Yale Univ. Interdepartmental Neurosci. Program, New Haven, CT

Abstract: The ability to detect and respond to threats is critical for survival, but dysfunction of threat circuits may result in anxiety or trauma-related disorders. While neural circuits underlying threat learning have been heavily investigated, our understanding of innate threat processing and how its representation might differ from learned fear is limited. Recent work evaluating human responses to visual threats in virtual reality found that height threat was the only visual stimulus to induce peripheral markers of arousal. Earlier literature has demonstrated both human infants and rodents avoid the edge of an apparent cliff. Despite this history and applicability to human studies, threat from physical height has not been adapted to test threat circuits using systems neuroscience approaches. Thus, we developed a virtual reality height threat task in which height threat can be manipulated to investigate neural circuits underlying threat-based decision-making. The medial prefrontal cortex (mPFC) is known to be activated by spatial proximity to threat and hypothesized to coordinate escape behaviors, while the locus coeruleus (LC) regulates arousal states. Thus, we hypothesized a LC - mPFC circuit may regulate decision-making in response to visual height threats.
In our task, animals were placed at the top of a 20” pole in an enclosed metal box. Visual stimuli were presented on a monitor beneath the mice and included checkerboard visual stimuli where one quadrant was visually proximal to the mouse, and the other three quadrants were projected as close (5cm) or far (20cm) from the proximal quadrant. The pole ends in a cone at which point mice must decide which quadrant to exit onto a Plexiglas surface. Animals receive 48 randomized trials where the target quadrant is rotated as well as the stimulus depth. “Safe” responses are those in which the mouse exits to the proximal, target quadrant.
When the difference between the target, “safe” quadrant and remaining quadrants is small, mice

choose the safe quadrant at chance levels, while mice choose the safe quadrant more often when the visual discrepancy is large. To specifically test the role of the LC - mPFC circuit in this process, we stimulated noradrenergic LC projections in the PFC and found this increased preference for the safe quadrant across all conditions, eliminating the difference between close and far conditions, suggesting this projection regulates threat-based decision making in this task. We next recorded calcium activity of single neurons while mice performed this task using Inscopix miniscopes with and without stimulation of LC terminals in PL. These data will be presented at the meeting.

Disclosures: S.M. Staszko: None. **E. Krishnamurthy:** None. **R. Lokanadham:** None. **A. Basu:** None. **A.P. Kaye:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.26/FF9

Topic: G.01. Neuroethology

Title: A dimensional framework of fear of heights reveals resilience and vulnerability to acrophobia

Authors: *X. YUAN;
Sch. of Life Sci., Hubei Univ., Wuhan, China

Abstract: A dimensional framework of fear of heights reveals resilience and vulnerability to acrophobia Yanting Shen[1,2], Ze Li[2], Wenbo Feng[2], Yongyan Li[2], Wei Shang[2], Tianyuan Zhu[3], Shuangyi Xie[2], Nan Wu[2], Liezhong Ge[4], Longnian Lin[2], Shuai Liu[2,5,] *, Yi-Hsuan Pan[2,] *, Xiao-Bing Yuan[1,2,] *[1]School of Life Science, Hubei University, Wuhan, 430062, China. [2]Key Laboratory of Brain Functional Genomics of Shanghai and Ministry of Education, Institute of Brain Functional Genomics, School of Life Science and the Collaborative Innovation Center for Brain Science, East China Normal University, Shanghai, 200062, China. [3]Shanghai Chengzhong Senior High School, Shanghai, 200434, China[4]Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou, 310063, China[5] Shanghai Changning Mental Health Center, Affiliated Mental Health Center of East China Normal University, Shanghai, 200335, China*Corresponding authors. Email: 20260008@hubu.edu.cn, yxpan@sat.ecnu.edu.cn, sliu@psy.ecnu.edu.cn

Abstract Acrophobia, the pathological extreme of fear of heights (FOH), is a common yet understudied anxiety disorder whose population variability and underlying mechanisms remain poorly understood. Here we combined a nationwide survey of 6,385 individuals across China with behavioral studies in mice to investigate the epidemiology and regulation of FOH. FOH exhibited a continuous distribution ranging from a previously unrecognized subgroup with no detectable height fear to severe FOH consistent with acrophobia. Psychometric analyses supported a unified latent structure and a refined five-level classification framework spanning

this spectrum. FOH varied with age and sex and was shaped by genetic predisposition, life experience and behavioral factors. Notably, regular physical exercise was associated with reduced FOH severity. Mediation analyses suggested that anxiety vulnerability and motor balance ability represent two major interacting pathways through which multiple biological and experiential factors influence FOH. Consistent with these findings, voluntary exercise reduced FOH-like behaviors in both wild-type and genetically susceptible mouse models. Together, our results support a dimensional view of FOH spanning resilience to acrophobia and highlight exercise as a candidate non-pharmacological strategy for modulating maladaptive height fear.
Key Words: Fear of heights, Acrophobia, Survey, Epidemiology, Experience, Anxiety, Motor balance, Exercise

Disclosures: X. Yuan: None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.27/FF10

Topic: G.01. Neuroethology

Title: Online prediction error drives sensory-motor control during escape sequences

Authors: *A. NAYAK, A. HEIN;
Computat. Biol., Cornell Univ., Ithaca, NY

Abstract: Understanding how the brain continuously integrates sensory information to guide real-time decision making remains a central challenge in systems neuroscience. Escape behavior offers an ideal window into this problem as it is often executed under extreme time pressure, and requires the brain to continuously evaluate sensory evidence and update actions accordingly. We developed a high-precision, closed-loop behavioral platform for zebrafish (Danio rerio) that tracks freely moving animals and uses feedback control to generate stimuli that update in real time based on the animal's movement.
Using this system, we show that ongoing escape is not governed by fixed thresholds on classical sensory variables such as retinal angular size or looming rate, which failed to predict whether fish continued or terminated escape. Instead, escape is controlled by sensory prediction error: the mismatch between observed visual feedback and the feedback predicted from the animal's own locomotion. Fish continuously monitor whether their evasive movements are effectively reducing threat. When escape movements fail to shrink the predator's retinal image as expected, escape continues; when they succeed, escape terminates. This computation also explains a striking behavioral dissociation we observed in experiments where fish directly targeted by a virtual predator sustain escape, while nearby non-targeted fish rapidly suppress their responses despite experiencing comparable visual inputs.
Our experiments suggest that evasion maneuvers are driven, at least in part, by a continuously updated estimate of prediction error, enabling the animal to evaluate the efficacy of its own

motor actions in real time. That such a mechanism operates in one of the most evolutionarily conserved behaviors (visual escape maneuvers) in vertebrates suggests that feedback control that relies on a discrepancy between predicted and observed sensory input may be a fundamental organizing principle of sensorimotor circuits. Our ultra low-latency closed-loop experimental framework provides a principled approach for identifying the sensory-motor algorithms implemented by brain circuits, providing a strong quantitative foundation for future work on the neural mechanisms of online prediction and evaluation during behavioral control.

Disclosures: A. Nayak: None. **A. Hein:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.28/FF11

Topic: E.07. Visual Sensory-Motor Processing

Support: DOD internal grant

Title: VR Flight Simulation and Multi-Echo fMRI: Mapping Multisensory Integration in Fighter Jet Pilots

Authors: *J. SHAO[1], E. LONG[1], S. YALEWAYKER[2], J. HOWARD[1], H. YALEWAYKER[2], M. P. TURNER[3], K. SODERLUND[1], C. VOJTA[1], T. YUAN[1], H. MORRIS[1];
[1]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Walter Reed Natl. Military Med. Ctr., Bethesda, MD; [3]Univ. of Texas at Dallas, Dallas, TX.

Abstract: Motivation/problem statement: Expertise-mediated fine motor tasks, such as piloting aircraft, require complex multisensory processing. However, the functional neurological network architecture responsible for integrating these cognitive and motor demands remains poorly understood. Functional MRI (fMRI) combined with virtual reality simulation (VR-sim) offers a unique opportunity to map these network relationships. This study utilized an in-scanner VR flight simulator to map stable task-associated networks in active-duty pilots and correlate network connectivity with real-time psychomotor performance. **Methods:** Thirteen expert fixed-wing pilots (12M, 1F) performed a Vertical S controlled climb/descent maneuver (regular oscillation between two flying altitudes). Active and resting-state fMRI data were processed using AFNI. A linear mixed-effects model identified task-associated networks by comparing global functional connectivity (gFC)—calculated as average voxel-wise whole-brain connectivity—between resting and VR-sim states. The model controlled for age, handedness, sex, and in-scanner motion. Psychomotor performance was quantified using the root-mean-squared error (RMSE) of the flown path relative to the ideal flight trajectory. **Results:** Differential gFC mapping (flight vs rest) revealed hyperconnectivity within the visual, prefrontal, right somatomotor, and temporal cortices, alongside hypoconnectivity in the left somatomotor cortex. Furthermore, superior task performance (lower RMSE) significantly

correlated with hyperconnectivity in visual networks and hypoconnectivity in the left somatomotor cortex. **Discussion & Conclusions:** The observed hyperconnectivity within visual networks supports the hypothesis that piloting relies heavily on the integration of dynamic visual inputs. Conversely, the task-associated hypoconnectivity in the somatomotor cortex is an unexpected finding. This warrants further exploration to determine whether it reflects global network suppression or localized network sharpening.

Figures

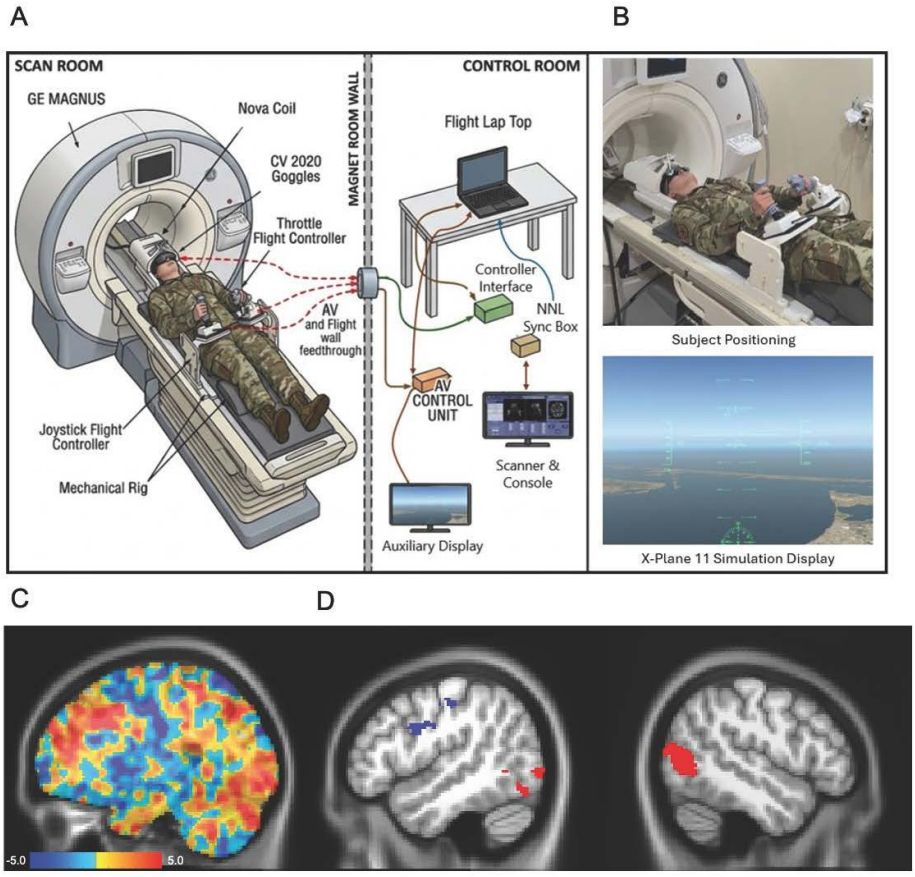


Figure 1) (A) Scans were conducted within a 3T GEHC MAGNUS MRI scanner. An MR-safe visual display and custom flight controllers were utilized. (B) VR-sim presented in an X-Plane 11 environment with standard flight gauge information. (C) Z-scored differential global functional connectivity between task and rest fMRI time series. Blue is hypoconnected and Red hyperconnected. (D) Bilateral task positive networks in Visual Cortex shown as red. Left lateralized task negative network in somatomotor cortex shown as blue. Networks thresholded for significance $p < 0.05$ and voxel size > 100.

Disclosures: J. Shao: None. **E. Long:** None. **S. Yalewayker:** None. **J. Howard:** None. **H. Yalewayker:** None. **M.P. Turner:** None. **K. Soderlund:** None. **C. Vojta:** None. **T. Yuan:** None. **H. Morris:** None.

Poster

PSTR320: Neuroethology: Sensory Motor Systems

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR320.29/FF12

Topic: E.07. Visual Sensory-Motor Processing

Support: K99EY037819

Title: Towards a novel method to investigate blink suppression in nonhuman primates

Authors: *S. M. WILLETT[1], S. E. SCHMITT[2], M. A. SMITH[2], J. MAYO[1];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Visual sensitivity decreases five-fold during an eye blink, a phenomenon known as blink suppression. Blink suppression is thought to facilitate visual continuity across the large full-field luminance changes induced by an eye blink. Although it is assumed that an active neuronal mechanism (e.g. corollary discharge) is responsible for blink-induced changes in perceptual sensitivity, the origin of this neuronal signal and how it alters computations in the visual system remains unknown. The neurophysiology of blink suppression has remained largely unexplored because of the methodological challenges in blink suppression paradigms that require an eyelid-independent retinal stimulus. That is, to probe visual sensitivity during blink the visual stimulus cannot be confounded by eyelid closure. The psychophysical work that discovered blink suppression illuminated the retina through the mouth. However, this method is challenging to recapitulate in model organisms more amenable to neuronal recordings. In this study, we test the feasibility of a novel approach to interrogate the neuronal mechanisms of blink suppression in the non-human primate.

The first hurdle to overcome in establishing a non-human primate blink suppression paradigm is to present an eyelid-independent retinal stimulus. The rhesus macaque orofacial structure precludes mouth-based retinal illumination. Therefore, we hypothesized that a light positioned to shine through the thin bones that encase the orbit would be sufficient to illuminate the retina independently of the eyelid. We tested the feasibility of this novel retinal stimulation method in two anesthetized rhesus macaques. We positioned a high-powered, red LED (Thorlabs, Inc.) against the posterior aspect of the sphenoid bone. We confirmed that the LED was sufficient to illuminate the retina by observing light through the pupil. That is, light shone through the skull and retina and then exited the orbit through the pupil. We optimized the position of the LED by maximizing the observable light through the pupil. We then performed a craniotomy over the parafoveal region of primary visual cortex (V1) ipsilateral to the stimulated eye. We lowered a 16-channel V-probe (Plexon, Inc.) into V1 and recorded neuronal activity to the onsets and offsets of the LED. In both animals, we observed sharp onset and offset transients in V1 activity in response to the LED across multiple V1 recording channels. These responses were robust even at 5% of LED power (~50 mA). The strong responses of V1 neurons to the LED and the LED illumination observable through the pupil confirm the feasibility of this method for a blink suppression paradigm.

Disclosures: S.M. Willett: None. **S.E. Schmitt:** None. **M.A. Smith:** None. **J. Mayo:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.01/FF13

Topic: G.03. Stress and the Brain

Support: NKFIH EXCELLENCE program 151377
National Institutes of Health P30DA056410
EFOP-3.6.3-VEKOP-16-2017-00009
Marie Skłodowska-Curie grant agreement No.
Human Frontier Science Program (HFSP) Fellowship LT0059/2024-L

Title: Islands of Calleja granule cell-mediated control of affective behaviors

Authors: *D. DIMEN[1], S. C. PROKOP[2,1], S. SZABÓ[1], L. ZSICHLA[3], A. TOTH[4,2], V. MÜLLER[5], K. MACKIE[2], I. KATONA[2];
[1]Inst. of Exptl. Med., Budapest, Hungary; [2]Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [3]HUN-REN Res. Ctr. for Natural Sci., Budapest, Hungary; [4]Inst. of Mol. Life Sciences, HUN-REN Res. Ctr. for Natural Sci., Bloomington, IN; [5]Inst. of Biology, Eötvös Loránd Univ., Budapest, Hungary

Abstract: Granule cells of the Islands of Calleja (ICj) are abundant yet poorly investigated neurons in the ventral striatum. Here, we studied how chronic functional manipulation of ICj granule cell activity affects basal physiology, behavior under familiar low-stress conditions, responses to novelty and environmental exposure, avoidance/risk-assessment behavior, and coping responses to an acute challenge in male and female mice. Body weight did not differ between experimental and control animals, indicating no gross alteration in metabolism or general physiological status. Likewise, under familiar home-cage conditions, animals showed no significant differences in locomotion, velocity, rearing, thigmotaxis, or digging, suggesting preserved baseline behavior in a low-stress environment. In contrast, robust behavioral differences emerged when animals were challenged with novel or anxiogenic contexts. In the open field test, disruption of ICj granule cell activity elicited increased locomotion and rearing, together with enhanced grooming behavior. This increase in locomotor activity was most pronounced during the initial phase of testing, pointing to an enhanced early response to novelty rather than stable hyperactivity, and may reflect increased alertness, exploratory drive or reduced fearfulness. These mice also spent more time in the center zone and showed an increased center-distance/total-distance ratio, consistent with reduced avoidance of exposed areas. In the light-dark box test, affected mice spent more time and traveled greater distances in the light compartment. The doorway analysis was especially informative: although the total number of doorway visits was similar between groups, affected mice were less hesitant at the threshold and more likely to enter the light compartment fully, suggesting reduced cautious risk assessment and increased risk-taking. In stress-coping assays, affected mice showed reduced immobility time and fewer immobile episodes in the forced swim test, with a similar reduction in passive coping

observed in the tail suspension test, consistent with a shift from passive toward active coping under acute challenge. Together, these findings indicate that ICj granule cells contribute to behavioral restraint in uncertain situations while leaving baseline behavior largely intact.

Disclosures: D. Dimen: None. **S.C. Prokop:** None. **S. Szabó:** None. **L. Zsichla:** None. **A. Toth:** None. **V. Müller:** None. **K. Mackie:** None. **I. Katona:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.02/FF14

Topic: G.03. Stress and the Brain

Support: HFSP Fellowship LT0059/2024-L
EU Horizone, Marie-Curie grant agreement No 101270269
NIH P30DA056410
NKFIH EXCELLENCE program 151377
National Laboratory of Translational Neuroscience Project no. RRF-2.3.1-21-2022-00011

Title: Phylogenetically conserved molecular and cellular organization defines the Islands of Calleja in the mouse, dog, monkey and human ventral striatum

Authors: *S. C. PROKOP[1,3], M. VÁMOSI[3], S. SZABÓ[3], L. ZSICHLA[3,4], C. SHUMAKER[1,3], L. BARNA[1], A. D. TOTH[1], D. DIMEN[3], B. BARTI[3], E. HORVÁTH[3], P. SZOCSICS[3], K. CZEIBERT[4], I. KACSKOVICS[4], V. MÜLLER[4], H. CHENG[1], D. P. KENNEDY[1], K. MACKIE[1,2], I. KATONA[1];
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Abstract: Although the Islands of Calleja (ICj) was first described in the basal forebrain more than a century ago, it remains one of the least studied structures of the mammalian brain. This limited recognition likely stems from its complex architecture, comprising numerous small and spatially dispersed cell clusters that are challenging to resolve in standard histological preparations or by in vivo methods. Consequently, this enigmatic brain region is not well defined in major anatomical atlases, including those of the human brain. Moreover, knowledge of the molecular organization and cellular architecture of the ICj in the mammalian brain remains incomplete, restricting efforts to define the translational relevance and therapeutic potential. In the present study, we systematically examined the gross anatomical properties and cytoarchitecture of the ICj across mouse, dog, monkey, and human using single-cell transcriptomic data analysis and multiscale anatomical characterization. We provide evidence for strong phylogenetic conservation in the molecular identity, cellular composition, and spatial

organization of the ICj across three lineages of mammals (rodents, carnivores and primates). Moreover, we demonstrate that ICj granule cells, the principal neuronal population of this brain circuit, constitute a substantial fraction of ventral striatal neurons, comparable in abundance to major medium spiny neuron subtypes in the nucleus accumbens. Our data also show that the ICj contains cholinergic cells and the traditional GABAergic striatal interneuron classes, further underscoring its organizational complexity and integration within ventral striatal circuitry. Together, these findings establish the ICj as a conserved component of the basal ganglia and provide a cross-species framework for investigating its role in striatal function and psychiatric disorders.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.03/FF15

Topic: G.03. Stress and the Brain

Support: Dean's Research Initiative at the College of Behavioral and Social Sciences

Title: Interplay between Social Isolation, Stress, and Serotonin in Crayfish

Authors: *K. BALAMURUGAN[1], H.-Y. JEON[2], J. HERBERHOLZ[2];
[1]Neurosci. and Cognitive Sci., [2]Psychology, Univ. of Maryland-College Park, College Park, MD

Abstract: Social isolation is considered a powerful stressor, associated with severe mental health disorders, and recognized to disrupt the gut-brain axis. How social isolation relates to stress, alters neurochemistry, and modifies behavior, however, remains poorly understood. To investigate the effect of social isolation on hemolymph (i.e., blood) glucose, a stress biomarker in crustaceans, we isolated (ISOs) adult crayfish for 7 days and compared them to communally housed animals (COMs). Contrary to our expectation, we found that glucose levels were similar between ISOs and COMs, suggesting that short-term isolation did not lead to a strong stress response. We then assessed preference in a light-dark two-chamber assay, a measure of anxiety-like behavior in crayfish, after inducing additional stress in ISOs. Despite an increase in glucose

after stressing the animals, there were no differences in light-dark preferences between stressed and unstressed ISOs, indicating that elevated stress did not affect behavioral decisions. Serotonin (5-HT) plays a role in the crustacean stress axis, as it triggers the release of crustacean hyperglycemic hormone, a precursor for glucose. As such, we performed electrochemical measurements of 5-HT in the hemolymph of COMs and ISOs in crayfish of two different genera: Procambarus and Faxonius. While COMs showed similar concentrations of 5-HT, Procambarus exhibited highest concentrations of 5-HT after 7 days of isolation, whereas Faxonius ISOs showed highest levels after 1 day of isolation, revealing species-dependent 5-HT dynamics following social isolation. To better understand how gut-derived 5-HT along the gut-brain axis might be involved in this process, we performed hematoxylin and eosin (H&E) staining of hindgut sections, which revealed a significant decrease of gut integrity in ISOs compared to COMs. Since social isolation affected hormonal 5-HT levels and gut health, we supplemented food with tryptophan (TRP), a precursor for 5-HT, and measured light-dark place preference again. The results paralleled species-specific 5-HT dynamics, as the TRP supplement had little effect on the behavior of Procambarus, but increased the time spent in the light chamber for TRP-fed Faxonius. Lastly, we observed an increase 5-HT in the hemolymph after TRP-supplemented diet, suggesting that fluctuations in hormonal 5-HT might be due to increased gut-derived 5-HT biosynthesis. Together, the results decouple the relationship between stress and 5-HT in crayfish, and they demonstrate complex, species-dependent interactions between social isolation, 5-HT, and corresponding behavior, possibly mediated by the gut-brain axis.

Disclosures: K. Balamurugan: None. **H. Jeon:** None. **J. Herberholz:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.04/FF16

Topic: G.03. Stress and the Brain

Support: Towsley Endowment for the Sciences

Title: Stress alters the frequency and stereotypy of grooming behavior in Drosophila melanogaster

Authors: M. RAMIREZ CORTES, A. HANSON, C. LIN, ***E. D. HOOPFER**;
Carleton Col., Northfield, MN

Abstract: Animals and humans engage in repetitive self-directed behaviors, such as grooming, in response to stress. In humans, excessive grooming can become pathological during periods of chronic stress and in several neuropsychiatric disorders, yet the neural mechanisms linking stress and grooming remain poorly understood. To investigate the link between stress and self-grooming, we examined how three stressors, heat exposure, social defeat, and social isolation, affect grooming behavior in *Drosophila melanogaster*. Male flies exposed to heat showed

increased spontaneous grooming during and after stress exposure, accompanied by less stereotyped grooming sequences. In contrast, socially isolated males exhibited reduced grooming but no change in stereotypy. Social defeat had no detectable effect on either the amount or sequencing of grooming behavior. Together, these findings demonstrate that grooming responses in *Drosophila* depend on the nature of the stressor and establishes a foundation for dissecting the neural and genetic mechanisms that link stress to self-directed behaviors.

Disclosures: M. Ramirez Cortes: None. **A. Hanson:** None. **C. Lin:** None. **E.D. Hoopfer:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.05/FF17

Topic: G.03. Stress and the Brain

Title: Multidimensional neurobiological symptom patterns in benzodiazepine withdrawal

Authors: *V. MADHAVA;
Brain Body Med., New York, NY

Abstract: Benzodiazepines arewidely used, and their discontinuation can produce diverse neurological,psychiatric, autonomic, sensory, and somatic symptoms. Despite their clinicalimportance, the organization of these withdrawal symptoms remains poorlycharacterized. In this exploratory cross-sectional study, baselineobservational data from 39 patients enrolled in a specialty benzodiazepinetaper program were analyzed using a structured 233-item withdrawal symptomquestionnaire; demographic data were available for 38 patients (mean age 48.9 ±14.5 years, 52.6% female). Symptoms were mapped onto five pre-specifiedmechanistic axes reflecting candidate neurobiological and neuroimmune pathways:corticotropin-releasing hormone (CRH)/adrenergic, excitatory-neuroinflammatory(ENI), autonomic, basal ganglia-cerebellar (BG/Cer), and mast-cell activationoverlap (MCAS-overlap). For each patient, symptoms rated ≥7/10 were talliedacross axes to characterize the relative distribution of severe symptomburden. Symptoms showed greater organization than expected underburden-preserving null models (mean inter-symptom |r| 0.1717 versus 0.1305,p≈0.0002), with parallel analysis supporting a multidimensional pattern ofsymptom variation. Symptom burden varied substantially across individuals andinvolved multiple candidate systems. Relative predominance was evenly dividedbetween CRH/adrenergic and ENI, each ranking highest in 14 of 39 patients; 4showed autonomic predominance, while 7 had low severe-symptom burden. BG/Cersymptoms occurred but were not predominant in this cohort. MCAS-overlapfeatures occurred in 22 of 39 patients (56.4%) and were distributed acrosssymptom-burden patterns. These findings suggest that benzodiazepine withdrawalis characterized by overlapping, multidimensional patterns of symptom burdenacross candidate neurobiological systems. Mapping symptom burden across

thesecandidate systems may provide a framework for studying withdrawal heterogeneityand for testing the biological mechanisms that may contribute to differentsymptom patterns.

Disclosures: V. Madhava: None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.06/FF18

Topic: G.03. Stress and the Brain

Support: NIMH R01MH112739

Title: Neuroanatomy of a tachykinergic circuit in the central extended amygdala

Authors: *E. M. WAINMAN[1], M. S. ANTONY[1], A. EHSAN[1], M. GILL[1], A. T. CHESLER[2], A. C. JACKSON[1];
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Abstract: Tachykinins are a family of neuropeptides that function as both neurotransmitters and neuromodulators, regulating a broad range of physiological processes, including cardiovascular function, inflammation, and the modulation of mood and stress. The neurokinin-3 receptor (NK3R), encoded by *Tacr3*, is a G protein-coupled receptor that preferentially binds neurokinin B (NKB), which is encoded by *Tac2* in rodents. Our previous work identified an NKB/GABAergic circuit within the central extended amygdala (CEA), in which *Tac2*-expressing neurons of the bed nucleus of the stria terminalis (BNST) and central amygdala (CeA) project in parallel to NK3R-expressing neurons in the lateral hypothalamus (LHA) and to additional downstream targets, including the ventral tegmental area (VTA), periaqueductal gray (PAG), and parabrachial nucleus (PBN). However, the brain-wide distribution of *Tacr3*-expressing neurons and the identity of *Tacr3*-expressing populations that may serve as downstream targets of CEA *Tac2* projections remain poorly characterized. To address this gap, we utilized a novel *Tacr3*-Flpo knock-in mouse line to visualize *Tacr3*-expressing populations. We validated this model using fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) to confirm the specificity and penetrance of recombinase expression. Whole-brain *Tacr3* expression was then mapped using tissue clearing and light-sheet microscopy, revealing broad but regionally enriched expression throughout the mouse brain. Subsequent IHC analyses identified cellular markers associated with previously unrecognized *Tacr3*-enriched neuronal populations across multiple brain regions. Having established the anatomical distribution and cellular identity of *Tacr3*-expressing populations, we employed dual-fluorescent anterograde viral tracing to examine the spatial relationship between CEA *Tac2* projections and *Tacr3*-expressing neurons within downstream target regions. We further used dual-fluorescent retrograde viral tracing to validate BNST and CeA *Tac2* projections and

determine whether individual *Tac2* neurons collateralize to multiple targets or whether distinct *Tac2* neuronal populations project to specific downstream regions. Collectively, these studies establish the *Tacr3*-Flpo mouse as a genetic tool for investigating *Tacr3*-expressing neuronal populations in the mouse brain and provide a foundation for future mechanistic studies of CEA NKB-NK3R signaling.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.07/FF19

Topic: G.03. Stress and the Brain

Support: 1R21MH136446
1R15HD110925

Title: Anatomical mapping of medial OFC circuits implicated in stress-induced aggression

Authors: *M. ADJEI[1], J. C. NORDMAN[2];
[1]Southern Illinois Univ. Carbondale, Carbondale, IL; [2]Physiol., Southern Illinois Univ., Carbondale, IL

Abstract: The orbitofrontal cortex (OFC) plays a critical role in decision-making, reward learning, and emotional regulation and is profoundly impacted by traumatic stress. Using a rodent model, we recently found that traumatic stress recruits excitatory medial OFC (mOFC) neurons to alter social behavior and promote persistent aggression. However, the afferent and efferent organization of mOFC networks, particularly across excitatory and inhibitory neuronal populations, remains poorly defined. Here, we used viral tracing approaches to map the input-output connectivity of the mouse mOFC. To begin, the mOFC of wild-type C57BL/6J mice was co-injected with an anterograde tracer, pAAV1-hSyn-EGFP, and a retrograde tracer, retro-pAAV-hSyn-mCherry, to broadly label mOFC inputs and outputs. To map excitatory connectivity, a separate cohort received pAAV1-CaMKIIα-EGFP and retro-pAAV-CaMKIIα-mCherry injections into the mOFC. To map inhibitory connectivity, vGAT-Cre mice received Cre-dependent viral tracers, pAAV1-hSyn-DIO-EGFP and retro-pAAV-hSyn-DIO-mCherry, targeted to the mOFC, enabling GABAergic-restricted labeling from the mOFC injection site. Preliminary analyses identified dense reciprocal connectivity between the mOFC and regions associated with stress-related changes in social and aggressive behavior, with distinct excitatory and inhibitory labeling patterns. These findings suggest that mOFC circuits are anatomically positioned to integrate stress-, affect-, and social-information streams that may contribute to persistent, maladaptive behavior. Future studies will test the causal roles of these distinct circuits in stress-induced aggression and related forms of maladaptive social behavior.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.08/FF20

Topic: G.03. Stress and the Brain

Support: NIMH intramural, MH002386

Title: Medial Prefrontal PACAPergic Projections to CRH^{PVN} Neurons Orchestrate Temporally Distinct Stress Response Programs via Cyclic AMP Signaling

Authors: *S. Z. JIANG[1], W. BRANCALEONE[1], J. WOLCOTT[2], C. R. GERFEN[1], A. LUTAS[2], L. E. EIDEN[1];
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Abstract: Stress responses unfold across distinct temporal domains, from rapid endocrine and behavioral reactions to slower transcriptional and endocrine adaptations. Here we characterize the signaling properties of medial prefrontocortical (mPFC) PACAPergic projections that synapses onto corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of hypothalamus (PVN). PACAP-driven cyclic AMP (cAMP) signaling in CRH^{PVN} mediates short-term behavioral responses to acute stress, and to prime long-term adaptation to chronic stress. These effects are independent of the non-cAMP-dependent CRH release from the median eminence that elevate circulating corticosterone (CORT). A $PACAP^{mPFC}$ projection to CRH^{PVN} neurons was demonstrated by monosynaptic rabies tracing. Intra-PVN infusion of PACAP1-38 increased *cfos* and *crh* mRNA in CRH^{PVN} neurons, effects blocked by expressing a constitutively active phosphodiesterase (PDE4D-cat). Brief footshock rapidly induced grooming behavior and cFos activation in CRH^{PVN} neurons; both responses were blocked by PDE4D-cat expression and mPFC-specific PACAP deletion. Elevation of cAMP by optogenetic activation of blue light-inducible adenylate cyclase (biPAC) in CRH^{PVN} neurons induced grooming. Its onset and duration coincided with exposure to blue light. Prolonged biPAC stimulation directly increased *cfos* and *crh* transcription in CRH^{PVN} neurons, an effect not observed with shorter stimulation protocols. This occurred without an increase in circulating CORT levels, consistent with lack of inhibition of CORT elevation by expression of PDE4D-cat or PKI in CRH^{PVN} neurons after psychogenic stress. Restraint stress of sufficient duration causes both cfos activation and *crh* transcription, and both are cAMP- and PKA-dependent. Elevation of *crh* transcription is required for maintenance of CORT elevation in the face of restraint stress prolonged for several hours or repeated over several days. Chemogenetic inhibition of $PACAP^{mPFC\rightarrow PVN}$ neurons attenuated cFos induction in CRH^{PVN} neurons following prolonged restraint stress without affecting acute CRH release, phenocopying the effects observed after deletion of PACAP from mPFC→PVN projections. Cyclic AMP elevation in CRH^{PVN} neurons mediates immediate coping behaviors, in a reversible manner, but, if sustained, engages transcriptional programs that support

neuroendocrine response resilience. These findings identify cAMP signaling in CRH^{PVN} neurons, driven by PACAP release under cortical control, as a temporal organizer of stress responses.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.09/FF21

Topic: G.03. Stress and the Brain

Support: NSF GRFP
R21AA031101
P50AA017823
SUNY Empire Innovation funds

Title: Distinct Locus Coeruleus to Medial Prefrontal Cortex Circuit Patterning in Male and Female Mice is Altered by Chronic Ethanol

Authors: *M. V. SCROGER[1], K. VO[1], M. SIDDIQI[1], M. MUNEEB[1], A. LISS[1], N. OROZCO[1], G. FUMAROLA[1], J. R. BAGLEY[2], F. P. VARODAYAN[1];
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Abstract: The locus coeruleus (LC)→dorsolateral prefrontal cortex (dlPFC) circuit plays a critical role in executive function and stress regulation, both of which are behavioral domains that are disrupted in alcohol use disorder (AUD). Within this circuit, norepinephrine (noradrenaline; NE) serves as a key neuromodulator of dlPFC activity, exerting state-dependent control over attention, cognitive flexibility, and arousal. As such, pharmacological blockade of α1 and β adrenergic receptors (ARs) can reduce alcohol consumption, craving, and anxiety in individuals with AUD. Despite the central role of LC-derived NE signaling in dlPFC function, the impact of chronic alcohol exposure on LC→dlPFC circuit function remains poorly understood. Defining how alcohol-induced adaptations within this circuit contribute to cognitive and behavioral dysfunction may provide new insight into the neurobiology of AUD. We first assessed basal sex differences in the equivalent LC→medial PFC (mPFC) circuit in C57BL/6J mice using retrograde fluorescent tracing and found females possess a greater percentage of LC neurons that project to the mPFC than males. We next examined the effects of forced abstinence following voluntary two-bottle choice ethanol drinking (IA2BC) on mPFC NE signaling. To accomplish this, we assessed glutamate transmission using *ex vivo* electrophysiology and AR gene expression using quantitative polymerase chain reaction. Short-term abstinence from IA2BC sex-dependently altered prelimbic mPFC layers 2/3 and 5 NE-induced increases in glutamate release, and these sex- and layer-specific effects were mediated by a mixture of α1 and β ARs. Short-term abstinence also altered mPFC α2A AR mRNA levels, while longer-term

abstinence affected mPFC α1A mRNA. Of note, AUD produced similar changes in human dlPFC AR transcripts. These findings highlight distinct alcohol-related changes in the LC→mPFC circuit and mPFC NE system in male and female mice. These neuroadaptations likely drive LC-NE dysfunction and dlPFC-dependent craving and relapse behaviors, highlighting this pathway as a critical therapeutic target for AUD.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

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Topic: G.03. Stress and the Brain

Support: NSF Graduate Research Fellowship Program (NSF-GRFP)
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Title: Hypothyroidism alters neural response to acute social defeat stress

Authors: *J. Y. CHEUNG[1], A. L. FALKNER[3], C. J. PENA[2];
[2]Princeton Neurosci. Inst., [1]Princeton Neurosci. Inst., Princeton, NJ; [3]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Hypothyroidism is commonly associated with a depressive mental state, while hyperthyroidism is associated with restlessness, anxiety and psychosis. In rodent studies, stress influences thyroid hormone (TH) release, and alterations to TH or its receptors (THRs) lead to a range of behavioral and affective changes, such as in exploratory behavior, fear learning, and learned helplessness paradigms. Despite aforementioned associations, there still is a lack of research directly examining TH's effects on how animals respond to ethologically-relevant stressors, especially at the levels of brain-wide network dynamics. To fill this gap, I conducted a brain-wide screening of c-Fos as a proxy for neural activity during social defeat stress (SDS), a well-established naturalistic stress paradigm, in hypothyroid mice versus controls. Adult male C57/BL6 mice were either rendered hypothyroid via propylthiouracil (PTU) diet replacement, or kept on regular diet as controls. At the end of the month-long treatment period, mice were tested on exploratory behaviors, and subjected to a single bout of SDS with a larger aggressor before tissue collection for whole-brain immunohistochemistry via iDISCO+. Hypothyroid mice expressed a low-exploration, low-velocity phenotype in the open field test (OFT), which is in line with both clinical expectations and existing rodent literature. They exhibited no significant behavioral differences during SDS, but whole-brain immunohistochemistry identified diffuse differences in brain-wide c-Fos expression that are distinguishable via machine learning classifiers. Interestingly, while the symptomatology of hypothyroid patients evokes the image of

a depressed neural state, certain brain regions (such as the periaqueductal gray) demonstrated increased reactivity to SDS in hypothyroid mice. Furthermore, these results are in agreement with an out-of-sample comparison from an earlier pilot study conducted in the same lab. In summary, hypothyroidism does not lead to a blanket depression of neural activity, but instead shifts network activity to an altered state. As these results cannot be explained by significant behavioral differences during SDS, they instead suggest alterations to internal neural responses that could influence post-stress learning and recovery. Future studies should examine whether neural and behavioral profiles would continue to diverge during post-stress recovery, or in an extended chronic stress paradigm. Additionally, we are currently exploring whether transient hypothyroidism in development also leads to comparable changes.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

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Program #/Poster #: PSTR321.11/FF23

Topic: G.03. Stress and the Brain

Support: Boehringer Ingelheim Fonds PhD Fellowship
Hope for Depression Research Foundation

Title: Hormonal regulation of stress resilience through ERα-dependent plasticity mechanisms

Authors: *C. A. MCLAIN[1], C. BLASCHKE[1], A. CUNNINGHAM[3], M. ESTILL[1], T. M. GYLES[6], L. HOLT[4], O. ISSLER[5], B. T. KIPP[1], V. KONDEV[1], G. ROJAS[2], E. J. NESTLER[7]; [2]Nash Family Dept. of Neurosci. and Friedman Brain Inst., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Neurosci. Dept., [5]Neurosci., [3]Mount Sinai Sch. of Med., New York, NY; [6]Friedman Brain Inst., [7]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Sex differences are evident in the prevalence and mechanisms of stress-related psychiatric disorders. Women experience these disorders at higher rates than men, and fluctuations in ovarian hormones are associated with changes in symptomatic prevalence and severity. These differences are mirrored in animal models, in which females exhibit greater stress susceptibility and behavioral responses vary across the estrous cycle. Despite this, our understanding of the mechanisms driving sex- and hormone-dependent differences in stress responses remains limited. We first asked whether stress differentially affects brain-wide neuronal activity in male and female mice using brain clearing and immunolabeling for FOS.

This unbiased approach revealed markedly stronger FOS induction in response to stress in males across the brain. The nucleus accumbens (NAc), a key stress/reward circuitry node, is among the most strongly activated regions in males, yet showed no response in females. To determine whether hormonal or chromosomal factors drive these sex differences, we used the four-core genotype mouse model, in which gonadal and chromosomal sex are dissociated. We found that hormonal sex drives sex differences in behavior and NAc transcription; specifically, the presence of ovaries increases stress susceptibility, with estradiol as a prominent upstream regulator of differentially affected genes. Estrogen regulates transcriptional programs in the brain through its nuclear receptors, yet the role of its genomic signaling pathway in shaping stress responses is poorly understood. To address this, we used CUT&RUN to characterize estrogen receptor alpha (ERα)-DNA binding sites in the NAc. We found that stress increases ERα-DNA binding in both sexes, but that this pathway is more abundant in males. Stress-induced ERα binding is enriched at genes involved in synaptic plasticity, leading us to hypothesize that this pathway protects against stress-induced plasticity deficits and promotes circuit flexibility in males, consistent with our brain-wide FOS mapping. Ongoing electrophysiological recordings will determine whether ERα+ NAc neurons in males are resilient to stress-induced deficits in synaptic plasticity. Manipulation of the pathway will determine whether it is causally involved in stress susceptibility. Together, these studies aim to provide a framework for understanding how biological sex shapes neural responses to chronic stress.

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Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

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Topic: G.03. Stress and the Brain

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Title: A reciprocal neuromodulatory circuit that controls the persistence of the stress state

Authors: *J. PARK;
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Abstract: Transient stimuli, such as stress, can trigger a persistent internal state that enables animals to reallocate behavioral strategies for survival. However, the neural mechanisms that transform transient stress signals into sustained behavioral states, and how these states are resolved, remain poorly understood. Here, we identify a long-range, reciprocal circuit between catecholaminergic and neuropeptidergic neurons in mice that control persistence of stress states. Using fiber photometry and dual-color miniscope imaging, we found that noradrenergic locus coeruleus (LC^{NA}) neurons and corticotropin-releasing hormone-expressing paraventricular hypothalamus (PVH^{CRH}) neurons exhibit persistent activity that extends beyond acute restraint stress. We demonstrated that both neural substrates reciprocally activate each other through neuromodulatory signaling. Furthermore, deletion of the *Dbh* gene in the LC using CRISPR-Cas9 largely disrupts the activity of PVH^{CRH} neurons. Projection-specific inhibition revealed that both LC^{NA}-PVH and PVH^{CRH}-LC pathways are required to sustain the stress state. In addition, we found that corticosterone (CORT) signaling in the LC^{NA}-PVH^{CRH} reciprocal circuit promoted termination of the stress state. Finally, the LC^{NA}-PVH^{CRH} reciprocal circuit is also required for sustaining a chronic stress state, providing a potential circuit-based explanation for stress-related disorders. Collectively, our findings define a neuromodulatory reciprocal circuit that transforms transient stress signals into a sustained internal state to drive adaptive behavioral shifts, while engaging endocrine feedback mechanisms that constrain persistence.

Disclosures: J. Park: None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.13/FF25

Topic: G.03. Stress and the Brain

Support: NIH R37 HD091280
ANR-24-CE16-4532
NIH U19 NS104653

Title: Diversity of Relaxin-3 neurons in the griseum centrale

Authors: M. TUFFERY[1], C. LAI[2], J. BOULANGER-WEILL[3], K. ARIYASIRI[2], M. E. HALPERN[2], G. FAINI[1], ***F. DEL BENE**[1];
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Abstract: The griseum centrale (GC) of the fish midbrain, homologous to the periaqueductal gray (PAG) region of the mammalian brain, has been implicated in fear responses, defensive behaviors and prey capture. The zebrafish PAG is enriched in neurons expressing the

neuropeptide Relaxin-3 (Rln3) encoded by rln3a and rln3b orthologues, but their properties have not been well characterized. Here we show that the rln3a-expressing population of the GC/PAG are molecularly, anatomically, and functionally diverse. Sparse labeling and electron microscopy reconstruction of individual rln3a neurons, reveal distinct cellular morphologies, with specific contralateral and ipsilateral arborization patterns and sites of dense core vesicles. A unique in vivo birthdating strategy indicates that the rln3a neurons arise in a temporally ordered manner. As a first step toward correlating neuronal subtypes with behavior, we examined the response of rln3a-expressing PAG neurons to visual cues presented to 6 dpf larvae. Unexpectedly, medially positioned neurons were activated in response to dark stimuli, consistent with known stress related behaviors of larval zebrafish to the onset of darkness. The response to the dark environment was sustained for at least one hour—potentially the longest sensory-evoked response recorded thus far in zebrafish. Silencing neuronal activity did not impair prey capture behavior or a looming evoked escape response. Current work is directed toward mapping the presynaptic inputs and postsynaptic targets of the distinct rln3a subtypes, as well as assessing the behavioral defects of rln3a and rln3b double mutants.

Disclosures: M. Tuffery: None. **C. Lai:** None. **J. Boulanger-Weill:** None. **K. Ariyasiri:** None. **M.E. Halpern:** None. **G. Faini:** None. **F. Del Bene:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.14/FF26

Topic: G.03. Stress and the Brain

Support: NIH R01HL173525
NIH F32HL172693

Title: Functional and transcriptional responses to chronic variable stress in the male and female posterior hypothalamus

Authors: *C. A. BOUCHET[1], S. A. PACE[2], E. C. PINSINSKI[3], J. H. RANDALL[2], M. M. LEONARD[2], C. E. VAAGA[2], B. MYERS[2];
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Abstract: Stressors are inevitable in daily life and stress exacerbates the risk for developing cardiovascular diseases, the leading cause of death globally. Stress-cardiovascular comorbidities are more prevalent in females, yet the neurobiological mechanisms underlying this sexual divergence are not well understood. The posterior hypothalamic nucleus (PH) is involved in endocrine stress responding, motivated behaviors, and cardiovascular function. Previous evidence indicates that neurons in the PH are activated by stress and are particularly sensitive to chronic variable stress (CVS). However, the effects of CVS on the PH have been exclusively

studied in males. Further, the functional alterations within this region have not yet been elucidated in either sex and could have meaningful impacts on stress responding. To address this, we performed neurophysiological, morphological, and transcriptomic analysis of the PH in adult male and female Sprague Dawley and Long Evans rats. Whole-cell patch clamp electrophysiology was conducted to determine plasticity of spontaneous firing properties within genetically-defined PH populations, allowing recordings specifically from glutamatergic and GABAergic PH neurons. Patched neurons were filled with biocytin for morphological analysis. Additionally, PH punches were analyzed for transcriptional changes following CVS using a targeted approach with Nanostring transcriptomics. This bulk transcriptional analysis was followed by targeted 10X spatial transcriptomics for single-cell spatial resolution of the CVS-induced changes. Results show sexually divergent functional plasticity within the PH. Functionally, after CVS we observed changes in resting membrane potential, action potential dynamics, excitability, and cell-type dependent spontaneous firing frequency in both males and females. Transcriptomic analysis identified increases in the expression of receptors involved in excitatory and inhibitory neurotransmission, specifically in the male PH. Together, data presented identify CVS-induced functional and transcriptional changes that can modulate the signaling within this stress-sensitive hypothalamic nucleus and define a subset of alterations that are sexually divergent. CVS-induced plasticity identified through these experiments may underlie differential susceptibility to stress-cardiovascular disease comorbidities.

Disclosures: C.A. Bouchet: None. **S.A. Pace:** None. **E.C. Pinsinski:** None. **J.H. Randall:** None. **M.M. Leonard:** None. **C.E. Vaaga:** None. **B. Myers:** None.

Poster

PSTR321: Stress-Modulated Pathways: Anatomy, Physiology, Neurochemistry

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR321.15/FF27

Topic: G.03. Stress and the Brain

Support: NIH R01 HL173525

Title: Cellular distribution and neurotransmitter phenotype of A11 dopamine neurons

Authors: *E. PINSINSKI[1], C. A. BOUCHET[2], J. RANDALL[2], B. POWERS[2], B. MYERS[2]; [1]Colorado State Univ., Fort Colllins, CO; [2]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: The posterior hypothalamus (PH) coordinates homeostatic integration, mediating autonomic, neuroendocrine, and behavioral outcomes. The PH is predominately glutamatergic but also contains GABAergic neurons and a dispersed dopaminergic population classified as A11. Previous literature examining A11 has focused on descending spinal projections that modulate sensorimotor functions and nociceptive processing. Prior studies consistently report that A11 does not express the dopamine transporter DAT, but studies have reported mixed results as to whether A11 neurons express vesicular glutamate transporter 2 (vGluT2) and/or

vesicular GABA transporter (vGAT). This leaves the neurotransmitter phenotype of A11 neurons and their potential to release fast-acting amino acid transmitters unclear. Therefore, this project aims to spatially map the cellular organization and neurotransmitter phenotype of the A11 population utilizing immunohistochemistry, 10x spatial transcriptomics, and RNAscope in situ hybridization in both male and female rats. Spatial mapping of A11 via tyrosine-hydroxylase (TH) immunoreactivity found TH+ cells spanning from the rostral PH to the rostral periaqueductal grey (PAG) with a small portion of cells residing in the subparafasicular (SPF) nucleus of the thalamus. The highest density of TH+ cells was identified in the rostral PH which then tapered caudally. The cellular distribution and total cell count were not different between sexes. The 10x spatial transcriptomic pilot consisted of 875 female A11 cells (6 sections, 4 females) and 570 male A11 cells (5 sections, 2 males). Preliminary analysis identified higher mean female expression of vGAT, GABA-synthesizing GAD2, dopamine receptors 2 and 3, as well as dopamine-synthesizing DOPA decarboxylase and TH. However, males displayed higher expression of vGluT2, dopamine receptor 1, NMDA subunit 1, and mGluR3. Given sex differences in A11 glutamate receptor expression, we investigated prefrontal cortex (PFC) as a glutamatergic input to A11. Genetic labeling of PFC presynaptic terminals revealed robust input throughout the A11 population. Ongoing RNAscope indicates most A11 neurons have the capacity to release either GABA or glutamate, with a minor population able to release both. Altogether, these findings highlight the potential for sex differences in A11 neurotransmission where females may have more capacity for GABA release and males may have more ability to release and respond to glutamate. Thus, this project provides a foundation for further investigation of sex-specific A11 circuit connectivity and potential contributions to homeostatic integration.

Disclosures: E. Pinsinski: None. **C.A. Bouchet:** None. **J. Randall:** None. **B. Powers:** None. **B. Myers:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.01/FF28

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Intramural Funds

Title: Gamma-Synuclein as a Marker for CB1R-Expressing Interneurons in the Basolateral Amygdala

Authors: *C. HIERS[1], J. CROW[1], S. PELAYO[1], N. WOODSIDE[1], L. S. ZWEIFEL[2], N. HAJOS[3], O. GUNDUZ CINAR[1], A. HOLMES[1];
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Abstract: Cortical inputs to the basolateral amygdala (BLA) are required for fear extinction, and enhanced endocannabinoid signaling modulates extinction-related synaptic plasticity through presynaptic cannabinoid receptor 1 (CB1R). However, the contribution of CB1R-expressing GABAergic interneurons, including cholecystokinin (CCK) interneurons, to extinction learning remains unclear, in part because available genetic strategies have lacked sufficient cellular specificity. To identify a more selective marker for this population, we examined gamma-synuclein (Sncg), which has been reported to strongly co-express with Cnr1 in hippocampal interneurons. Using RNAscope and immunohistochemistry, we characterized Sncg expression in the BLA and determined its overlap with inhibitory and excitatory cell markers. Sncg expression was found predominantly in GAD2-positive cells, with only limited overlap in Slc17a7-positive cells, indicating enrichment in GABAergic interneurons. Intersectional viral targeting confirmed that Sncg-expressing BLA cells are largely inhibitory and co-express CB1R. To test the functional relevance of CB1R signaling in these cells, we combined viral manipulations with fear extinction behavior. CRISPR-mediated disruption of Cnr1 in GABAergic interneurons impaired fear extinction, supporting a role for interneuron CB1R signaling in extinction learning. These findings identify Sncg as a useful marker for targeting CB1R-expressing interneurons in the BLA and provide a new strategy for dissecting how inhibitory microcircuits regulate fear extinction.

Disclosures: C. Hiers: None. **J. Crow:** None. **S. Pelayo:** None. **N. Woodside:** None. **L.S. Zweifel:** None. **N. Hajos:** None. **O. Gunduz Cinar:** None. **A. Holmes:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.02/FF29

Topic: H.01. Fear and Aversive Learning and Memory

Title: Opposing prefrontal-amygdala circuit dynamics govern context-dependent fear renewal and extinction

Authors: *J. LEE[1,2], E.-J. KIM[1], G. BYEON[3,4], J.-Y. AN[3,4,5,6], J. KOO[1,2];
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Abstract: Fear is an adaptive emotion essential for survival, enabling organisms to discriminate dangerous from safe contexts and generate appropriate defensive responses. However, dysregulation of this context-dependent fear discrimination is a key contributor to anxiety-related disorders. Extinction-based therapies are widely used treatments, yet their long-term efficacy is limited by a phenomenon known as fear renewal. Despite extensive research, the precise circuit-

specific mechanisms mediating fear renewal remain poorly understood. Using an ABC renewal paradigm, in which extinguished fear re-emerges in a novel context C, we compared behavioral and neural responses with ABB conditions where extinction memory is successfully retrieved. In this study, we investigated how distinct prefrontal cortex inputs to the basolateral amygdala (BLA) differentially regulate fear renewal. Using activity-dependent cell labeling in TRAP2 mice, we demonstrated that BLA neurons receiving prelimbic (PL) input during conditioning were preferentially reactivated during renewal, and this reactivation positively correlated with freezing behavior. Optogenetic inhibition of the PL-to-BLA circuit suppressed fear renewal, whereas inhibition of the infralimbic (IL)-to-BLA circuit promoted renewal. Fiber photometry revealed that PL-BLA activity was elevated during acquisition and renewal but suppressed during late extinction, while IL-BLA activity was selectively recruited during late extinction but silent during renewal, suggesting functionally dissociable roles in fear expression and extinction memory.Single-nuclei RNA sequencing of BLA cells further revealed that *Cck*, *Ctsl*, and *Fabp5* were upregulated in ABB extinction animals, whereas *Chst9* and *Sox2ot* were upregulated in ABC renewal animals, implicating distinct molecular programs in fear suppression and relapse. To further define the molecular identity of circuit-specific input-receiving BLA neurons, single-cell RNA sequencing was performed using anterograde trans-synaptic viral labeling.These findings collectively reveal circuit- and molecular-level mechanisms underlying fear renewal and extinction in PFC-BLA pathways.

Disclosures: J. Lee: None. **E. Kim:** None. **G. Byeon:** None. **J. An:** None. **J. Koo:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.03/FF30

Topic: H.01. Fear and Aversive Learning and Memory

Title: A New Locus of Fear Learning-Induced Plasticity: The Amygdalostriatal Transition Area

Authors: *D. MAGYAR[1], R. KARLÓCAI[1], N. HAJOS[2];
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Abstract: Canonical models of amygdala function propose that the lateral amygdala (LA) serves as the primary sensory input site during fear conditioning, relaying activity downstream to the basal amygdala (BA) and central amygdala (CeA). The role of the adjacent amygdalostriatal transition area (AStria) in this circuit has remained unclear. To address this, we performed in vivo silicon-probe recordings in awake, head-fixed mice during tone-footshock pairing, using a tone as the conditioned stimulus (CS) and a footshock as the unconditioned stimulus (US), to examine sensory stimulus-evoked responses and spiking plasticity. We found that tone presentation did not elicit significant increases in firing in BA or CeA neurons. In contrast, both the LA and the AStria showed robust, comparable responses to both the tone and the shock, with

similar firing rates, cluster proportions, and response profiles across all stimulus conditions. Using a two-CS discrimination paradigm, in which one tone was paired with the shock (CS+) and another was not (CS-), we found that subsets of neurons in both regions showed plasticity, with increased or decreased responses to CS, and these changes persisted into post-pairing recall. The distribution of plastic responses was comparable between LA and AStria. Together, these results identify the LA and AStria as a functionally parallel circuit that jointly processes CS and US signals during pairing, while BA and CeA neurons are not robustly recruited by these sensory stimuli. These findings challenge the canonical hierarchical model of amygdala information flow.

Disclosures: D. Magyar: None. **R. Karlócai:** None. **N. Hajos:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.04/FF31

Topic: H.01. Fear and Aversive Learning and Memory

Support: KHIDI grant RS-2024-00440099

Title: Central Amygdala GLP-1R Neurons Encode Aversive Valence to Suppress Feeding

Authors: *N. LEE[1], Y.-B. KIM[2], H. CHOI[1];
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Abstract: GLP-1 receptor agonists suppress appetite and reduce body weight, yet the limbic mechanisms underlying their effects on feeding remain incompletely understood. Feeding is not governed solely by metabolic need or satiety: bitter taste, visceral malaise, and threat can rapidly override hunger and suppress ingestion. Because the central amygdala (CeA) is a key region for aversive valence and affective learning, we examined whether GLP-1R-expressing CeA neurons (CeA Glp1r neurons) encode aversive valence during consumption and causally regulate the aversive suppression of feeding.
Using in vivo calcium recordings, including fiber photometry and miniscope imaging, we found that CeA Glp1r neurons exhibit valence-dependent dynamics during consumption, with decreased activity during sucrose intake and rapid activation during quinine intake. CeA Glp1r neurons were also activated by Exendin-4 (a GLP-1R agonist), suggesting that this population is responsive to both aversive feeding-related signals and pharmacological GLP-1R activation. Optogenetic activation of CeA Glp1r neurons was sufficient to induce negative affect-like facial expressions, real-time place avoidance, conditioned taste aversion, and acute suppression of ongoing feeding. Conversely, optogenetic inhibition of CeA Glp1r neurons blunted aversive behavioral responses, increasing quinine consumption and attenuating LiCl-induced conditioned taste aversion. Anatomical circuit mapping further revealed that CeA Glp1r neurons receive

monosynaptic inputs from the area postrema (AP), parabrachial nucleus (PBN), and insular cortex, and project to the nucleus accumbens (NAc), lateral habenula (LHb), and substantia nigra pars reticulata (SNr).
Collectively, our findings demonstrate that CeA Glp1r neurons encode aversive valence to regulate consumption. We propose that GLP-1R agonists may co-opt this intrinsic CeA valence-processing circuit, allowing aversive valence signals to contribute to appetite suppression.

Disclosures: N. Lee: None. **Y. Kim:** None. **H. Choi:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.05/FF32

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Intramural Research Funds

Title: Evaluating NECAB2 as a Marker for CCK/CB1R Interneurons in the Basolateral Amygdala During Fear Extinction

Authors: *N. WOODSIDE[1], J. CROW[3], M. XIA[2], E. VAN LEER[3], S. PELAYO[3], C. HIERS[3], L. S. ZWEIFEL[4], N. HAJOS[5], O. GUNDUZ CINAR[3], A. HOLMES[1];
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Abstract: Cortical inputs to the basolateral amygdala (BLA) are critical for fear extinction, and enhanced endocannabinoid signaling modulates extinction-related synaptic plasticity through presynaptic CB1 receptors (CB1Rs). However, the specific role of CB1R-expressing cholecystokinin (CCK) interneurons in the BLA remains unclear. Prior efforts to target these GABAergic interneurons using CCK-Cre-Dlx-FLpo mice lacked cellular specificity, labeling multiple non-CCK populations. Here, we used an intersectional viral strategy to test whether the calcium-binding protein NECAB2 could serve as a selective marker for CCK/CB1R interneurons in the BLA. NECAB2 has been reported to identify this population in the hippocampus, but its utility in the amygdala has not been established. Using viral promoter-based labeling, we characterized NECAB2-expressing cells in the BLA and examined their behavioral relevance during fear extinction. Necab2-driven expression was found primarily in GABAergic neurons, but showed limited specificity, with substantial co-labeling in NPY-, VIP-, and PV-expressing interneuron populations. In addition, CB1R expression was not enriched in NECAB2-positive interneurons. These findings indicate that NECAB2 is not a selective marker for targeting CB1R-expressing CCK interneurons in the BLA. Identifying more precise genetic tools for this population will be important for defining how inhibitory microcircuits regulate fear and

extinction learning and may inform therapeutic strategies for anxiety- and stress-related disorders.

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Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.06/GG1

Topic: H.01. Fear and Aversive Learning and Memory

Support: Z01ES090089

Title: Cholinergic signaling in the ventral hippocampus regulates adaptive threat responses

Authors: *S. WANG[1,2], K. D. STEVANOVIC[2], J. D. CUSHMAN[2], J. L. YAKEL[2];
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Abstract: The ability of animals to detect and properly respond to threats is critical for survival and maladaptive threat processing is strongly implicated in a wide range of neuropsychiatric disorders. The ventral hippocampus (vHipp) is a key neural hub that integrates contextual and emotional information during defensive behaviors. The vHipp is regulated by several neuromodulators, including acetylcholine (ACh), which modulates attention, learning, and behavioral state. Previous studies show that brain-wide cholinergic activity contributes to threat processing by enhancing fear learning and promoting defensive behaviors such as freezing and avoidance. However, the specific role of ACh signaling in the vHipp during threat responses remains unclear.To address this question, we combined fiber photometry with a genetically encoded fluorescent ACh sensor to monitor vHipp ACh dynamics in mice during a customized closed-loop escape-behavior paradigm. In this paradigm, mice were trained to freely explore an arena where they encountered different stimuli. We found that threatening stimuli, such as a rapidly expanding dark spot (“looming”) mimicking an aerial predator, produced a robust increase in vHipp ACh levels and triggered escape to a shelter, whereas a neutral auditory stimulus did not elevate ACh levels or induce escape. In addition, after mice were trained to associate the sound with an aversive foot shock, the conditioned sound alone elicited defensive responses including escape in the looming arena or freezing in an inescapable chamber. Temporal analysis revealed prolonged ACh increases during the conditioned sound, and transient increases when mice transitioned from freezing to escape attempts, suggesting that vHipp ACh signaling participates in both innate and learned threat responses. To further test how ACh regulates threat processing, we used optogenetic approaches to manipulate cholinergic input to the vHipp. Opto-stimulating ACh release increased exploratory behavior while also promoting escape to the shelter when the naive stimulus was presented. In addition, ACh stimulation

increased escape attempts during conditioned sound recall, whereas inhibition reduced these responses. Together, these results suggest that cholinergic signaling in the vHipp promotes rapid defensive responses by biasing animals toward a reactive state when encountering potential threats. This work identifies a neuromodulatory mechanism through which the brain dynamically regulates adaptive responses to environmental danger.

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Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

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Program #/Poster #: PSTR322.07/GG2

Topic: H.01. Fear and Aversive Learning and Memory

Support: HUN-REN Hungarian Research Network, Hungarian Brain Research Program (2017-1.2.1-NKP-2017-00002)
National Research, Development and Innovation Office (K131893)

Title: Basal amygdala neurons projecting to the dorsomedial striatum regulate cue-dependet fear

Authors: *Z. REEB[1,3], B. BRUZSIK[2,4], G. NAGY[1,4], D. MAGYAR[1,4], O. I. PAPP[1], C. PARDO-BELLVER[1], M. TOTH[2], J. M. VERES[1], E. GREGORI[1], M. ALICZKI[2], B. BARABAS[1,4], E. MIKICS[2], N. HAJOS[1,5,6];
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Abstract: The amygdala is a complex structure composed of many regions, yet the role of individual nuclei and especially neuronal populations targeting distinct downstream regions are not fully understood. We identified a transgenic mouse line, Arhgef6-Cre that expresses the recombinase in the anterior part of the basal nucleus (BAa) which hosts two largely separated principal cell populations projecting to the dorsomedial prefrontal cortex (dmPFC) and dorsomedial striatum (DMS). Inhibiting the function of Arhgef6-expressing BAa neurons resulted in an impairment in fear acquisition and its recall, without any major changes in anxiety-related behavior, sociability and operant learning. Pathway specific inhibition revealed that reducing the activity of BAa neurons projecting to the DMS largely recapitulated the results obtained in Arhgef6-Cre mice, whereas suppressing the function of BAa neurons projecting to the dmPFC reduced only freezing during contextual fear recall. Mapping the collateral systems of these two projection-defined populations using a synaptophysin-based labeling approach combined with control virus labeling revealed only minor differences in their broader output

patterns, suggesting that distinct collateralization is unlikely to be responsible for their differential roles in fear conditioning**.** In vivo electrophysiological recordings determined that footshocks excited more efficiently BAa neurons projecting to the DMS in comparison to those innervating the dmPFC. Our results thus imply that BAa neurons control conditioned fear by routing information preferentially towards the DMS and not dmPFC, whereas the other neuronal group projecting to the dmPFC contributes to contextual fear memory processes.

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Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

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Program #/Poster #: PSTR322.08/GG3

Topic: H.01. Fear and Aversive Learning and Memory

Support: Swiss National Science Foundation Grant #10.007.144

Title: The lateral amygdala presents CS signals to downstream circuits for plasticity and learning in associative memory

Authors: J. WU, O. KOCHUBEY, *R. SCHNEGGENBURGER;
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Abstract: The lateral amygdala (LA) has been identified as an important brain area for the integration of CS- and US-signals, and as a site of CS-plasticity in fear learning. This role of the LA was established in classical work in the rat model. Nevertheless, the role of excitatory neurons in fear learning specifically in the LA, as opposed to the adjacent basal amygdala (BA), has not been addressed in mice. Here, we use VGluT2Cre mice to selectively target LA excitatory neurons, combined with in-vivo optogenetics and in-vivo Ca2+ imaging with a miniature microscope, to study the role of the LA in auditory-cued fear learning. Imaging shows that a relatively small (5%) sub-population of LA-VGluT2+ neurons acquire tone (CS) responses during fear learning. This acquisition of a CS-response is caused by associative learning, as it is not present in control mice undergoing unpaired CS-US presentations. Surprisingly, optogenetic silencing of LA-VGluT2+ neurons during fear learning training or recall causes only small changes in the expression of a fear memory. We then employed optogenetic stimulation, to further investigate the behavioral roles of LA-VGluT2+ neurons. A weak stimulation regime (10 mW; 10 Hz trains interrupted every other second) did not induce marked behavioral changes in naive mice. Conversely, increasing the stimulus frequency to 20 Hz caused escape-like running of the mice, which might indicate a role of LA-VGluT2+ neurons in active coping, not further investigated here. Importantly, repeated pairing of weak optogenetic stimulation with footshocks led to the gradual appearance of a conditioned response (CR) - freezing, caused by the

optogenetic stimulation. One day later, the conditioned response caused by optogenetic activation of LA neurons was maintained. This indicates strong associative learning, in which - in the absence of an external CS - activity of LA-VGluT2+ neurons functions as a CS (hence, "internal CS"). Because it can be assumed that optogenetic stimulation will override the effects of possible plasticity occurring at the input synapses to LA neurons, we suggest that the associative learning upon activation of LA neurons must be caused by plasticity in downstream targets of the LA. It will be important to investigate the output connectivity of LA-VGluT2+ neurons, to address the underlying plasticity mechanisms.

Disclosures: J. Wu: None. **O. Kochubey:** None. **R. Schneggenburger:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.09/GG4

Topic: H.01. Fear and Aversive Learning and Memory

Support: STI 2030-Major Projects (2021ZD0202702)

Title: Hypothalamic-hindbrain circuit for consumption-induced fear regulation

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Abstract: To ensure survival, animals must sometimes suppress fear responses triggered by potential threats during feeding. However, the mechanisms underlying this process remain poorly understood. In the current study, we demonstrated that when fear-conditioned stimuli (CS) were presented during food consumption, a neural projection from lateral hypothalamic (LH) GAD2 neurons to nucleus incertus (NI) relaxin-3 (RLN3)-expressing neurons was activated, leading to a reduction in CS-induced freezing behavior in male mice. LHGAD2 neurons established excitatory connections with the NI. The activity of this neural circuit, including NIRLN3 neurons, attenuated CS-induced freezing responses during food consumption. Additionally, the lateral mammillary nucleus (LM), which received NIRLN3 projections, along with RLN3 signaling in the LM, mediated the decrease in freezing behavior. Collectively, this study identified an LHGAD2-NIRLN3-LM circuit involved in modulating fear responses during feeding, thereby enhancing our understanding of how animals coordinate nutrient intake with threat avoidance.

Disclosures: Q. Wang: None. **R. Sun:** None. **J. Hu:** None. **C. Li:** None. **X. Li:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.10/GG5

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant DK142148

Title: Parasubthalamic tac1-expressing neurons encode malaise signals that amplify conditioned taste aversion

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Abstract: Conditioned taste aversion (CTA) is a robust form of associative learning in which consumption of a novel flavor becomes associated with subsequent sickness, resulting in long-lasting avoidance of that flavor. Although CTA is highly adaptive for toxin avoidance, it can become maladaptive when unrelated sources of illness are incorrectly attributed to recently consumed foods, such as during chemotherapy-induced nausea. Current models of CTA circuitry emphasize visceral malaise signaling from brainstem nuclei, such as the lateral parabrachial nucleus (lPBN), to the central nucleus of the amygdala (CeA). However, additional integrative or modulatory components of this circuit remain poorly understood. Here, using male and female mice, we identify Tac1-expressing neurons in the parasubthalamic nucleus ($PSTN^{Tac1}$) as a previously unrecognized contributor to malaise signaling during CTA. We show that $PSTN^{Tac1}$ neurons are activated by multiple physiologically distinct malaise-inducing stimuli, as well as during conditioned flavor re-exposure. Using chemogenetic and optogenetic approaches, we demonstrate that activation of $PSTN^{Tac1}$ neurons is sufficient to support CTA formation, and projection-specific optogenetic stimulation further reveals that CTA acquisition is supported by a $PSTN^{Tac1}$-CeA but not a $PSTN^{Tac1}$-PBN pathway. Although inhibition of $PSTN^{Tac1}$ neurons did not attenuate CTA formation, this inhibition was associated with persistent malaise-related signaling in other PSTN populations and across broader CTA-associated circuitry, supporting the existence of distributed learning pathways. Together, these findings support a revised model of CTA circuitry in which $PSTN^{Tac1}$ neurons amplify brainstem visceral malaise signals before relaying them to limbic learning centers, particularly relevant to food aversions associated with chronic nausea.

Disclosures: B. Biever: None. **M. Carter:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.11/GG6

Topic: H.01. Fear and Aversive Learning and Memory

Support: PSC-CUNY
Clare Booth Luce Program, Henry Luce Foundation

Title: Safety cues engage theta communication in the prefrontal-sensory-attention network in both sexes

Authors: *R. KOLARIC[1], T. NABATIAN[2], E. LIKHTIK[3];
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Abstract: Post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) disproportionately affect women and are characterized by impaired safety signaling. The current gold-standard behavioral treatment is exposure therapy, which aims to reduce fear through nonreinforced exposure to fear cues, but leaves patients vulnerable to fear relapse. Safety conditioning offers an alternative by teaching that a cue predicts absence of threat, creating a conditioned inhibitor that suppresses fear. Notably, latent inhibition, in which pre-exposure reduces a cue's subsequent associability, also inhibits fear, although it is predicted to rely on distinct mechanisms. Few studies have directly compared safety vs latent inhibition in fear regulation, examined how these forms of inhibitory learning are acquired across sex or how they shift network communication in comparison to fear. To address these questions, we trained male and female mice on concurrent safety conditioning (SC) and latent inhibition (LI) to different auditory cues followed by fear conditioning to a light cue, and then tested the inhibitory properties of SC and LI tones using the fear summation test. We found that during learning the SC cue decreased fear of context but the LI cue had no effect, indicating that SC cue was an inhibitor of fear whereas the LI was not. We also saw that males showed lower defensive freezing during SC and LI than fear cues, but females showed equally high fear to all three cues. Then, during summation, SC and LI cues both suppressed fear, suggesting generalization of conditioned inhibition from the SC to the LI cue in a new context. To characterize network communication during summation, we recorded local field potentials from the infralimbic cortex (IL), basal forebrain (BF), basolateral amygdala (BLA), and primary auditory cortex (A1), and measured acetylcholine (ACh) release in the BLA using GRAB-ACh fiber photometry. GRAB-Ach recordings revealed a two-phase response, with a rapid cue-onset ACh release for all cues, and a sustained ACh release only during SC and LI cues. Analyses of theta (3-6Hz) oscillations complemented the photometry data, showing increased BF-to-BLA theta power communication during SC and LI cues. Analyses of theta communication across the network revealed two states: in the fear state, mice showed elevated IL-BF and IL-BLA theta coherence, whereas during the safety (but not LI) state there was elevated IL-A1 and BF-A1 theta coherence. Thus, we show increased sensory and attention processing during safety than fear or LI in both sexes.

Disclosures: R. Kolaric: None. **T. Nabatian:** None. **E. Likhtik:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.12/GG7

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH R01MH118441
Stanley Weiss Award in Experimental Psychology
Psychology Program Travel Award

Title: PV neurons in the ventral pallidum regulate fear extinction learning

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Abstract: Fear extinction reduces defensive responses to previously threatening stimuli, yet the circuits supporting this process remain incompletely understood. The infralimbic cortex (IL) is essential for extinction, with IL projections to the amygdala supporting extinction retrieval. In contrast, circuits mediating learning are less defined. We recently showed that IL projections to the ventral pallidum/substantia innominata (VP/SI) are preferentially engaged during extinction acquisition and that inhibiting this pathway slows learning. Thus, here, we investigate how the VP/SI partakes in extinction learning. First, using IL anterograde tracing and postsynaptic labeling, we found that IL terminals contact parvalbumin-expressing (PV) cells and, with lesser density, cholinergic (Ch) cells in the VP/SI. Next, using immunolabeling for the immediate early gene cFos in Ch or PV cells, we show that Ch activity is the same early and late in extinction. However, lower Ch activity in late extinction shows a trending correlation with better learning ($r(9)=0.53$, $R^2=0.28$, $p=0.09$), suggesting that Ch downregulation may reflect performance. On the contrary, PV activity increases in late extinction (Mann-Whitney, $p=0.057$), indicating that VP/SI PV activity may regulate extinction learning. To test this idea, we used PV-Cre mice and the inhibitory opsin eArch3.0-Cre (or eYFP-Cre) to inhibit VP/SI PV cells during extinction, which slowed learning (Group x Cue, $p<0.05$), indicating that VP/SI PV cells modulate extinction acquisition.Given the known role of GABAergic neurons in the generation of gamma oscillations, we next used local field potential (LFP) recordings to assess VP/SI high gamma (70-120Hz) dynamics during learning. We found that VP/SI high gamma power increased in late extinction (Early vs Late, Wilcoxon, $p<0.05$), consistent with enhanced GABAergic recruitment. We are currently combining optogenetic PV inhibition with LFP recordings in the VP/SI to determine whether PV cells are responsible for VP/SI fluctuations in high gamma. Taken together, our findings identify VP/SI PV neurons as key effectors promoting extinction learning and suggest that the IL-VP/SI pathway recruits this population to suppress defensive behavior. These results provide new insight into basal forebrain mechanisms regulating fear extinction and identify potential therapeutic targets for PTSD.

Disclosures: M.G. Sclar: None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.13/GG8

Topic: H.01. Fear and Aversive Learning and Memory

Support: ANR NEURAVOID ANR-21-CE37-0015
Brain and Behavior Research Foundation NARSAD Young Investigator award
Fyssen Foundation
Brain research Foundation

Title: Dopamine neurons calibrate proactive and reactive defensive behaviors in active place avoidance

Authors: *A. BESNARD;
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Abstract: Survival defensive behaviors emerge from distributed neural circuits that integrate spatial and temporal dynamics of threat imminence, internal states of emotion and prior experience. Defensive behaviors are highly conserved across species and distortions in threat imminence processing have recently been proposed as contributing factors in anxiety and fear-related disorders. Understanding the neural correlates of threat imminence processing, and their relationship to behavioral output may inform new strategies to combat anxiety and fear-related disorders. We developed a unified experimental preparation combining active place avoidance with markerless pose estimation to quantify multivariate defensive behaviors in mice. These behavioral motifs include avoidance, risk assessment, freezing, darting and escape across conditions of potential, acute, and immediate danger. Using brain-wide activity mapping, we identified distributed and partially overlapping anatomical networks whose recruitment reflects both behavioral output and danger state. Focusing on midbrain circuitry, we applied optical tools in freely moving subjects to assess the role of ventral tegmental area dopamine neurons in calibrating defensive behaviors across danger states. These experiments suggest that dopaminergic transmission biases defensive behaviors away from reactive responses (freezing) and toward proactive responses (avoidance, risk assessment) particularly during acute danger states when threat imminence is elevated. Leveraging this circuit-resolved framework, we further uncovered robust sexual dimorphism in the expression of mouse defensive behaviors. Female mice displayed greater reactive responses and also demonstrated differences in nucleus accumbens dopamine release upon active place avoidance. Current efforts are aimed at better understanding this sexual dimorphism within the nucleus accumbens at a functional level.

Disclosures: A. Besnard: None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.14/GG9

Topic: H.01. Fear and Aversive Learning and Memory

Support: Actuated Medical
NIH Grant MH122561

Title: Single unit recording of central amygdala and amygdalostriatal region during cue-evoked suppression of reward seeking

Authors: *K. ANDERSON[1], C. E. STELLY[3], J. P. FADOK[2];
[2]Psychology and Tulane Brain Inst., [1]Tulane Univ., New Orleans, LA; [3]Cell & Mol. Biol., Loyola Univ. New Orleans, New Orleans, LA

Abstract: Maladaptive and dysregulated valence processing are common features of many psychiatric illnesses, such as anxiety disorders, yet the neural mechanisms of this dysregulation remain unclear. To explore this, we used a cue-evoked conditioned suppression of reward seeking paradigm, which addressed both positive and negative valence processing simultaneously via a combination of operant learning and Pavlovian conditioning. In addition, we gathered single unit data in the behaving animals during this conditioned suppression paradigm through a probe implanted into the central amygdala (CeA) and amygdalostriatal region (Astr). This experimental design allowed us to record *in vivo* extracellular field potentials in the CeA and Astr while C57BL/6 mice are exposed to stimuli with both vegetive and positive valences simultaneously. Behavioral data was analyzed using DeepLabCut, an automated machine learning program, with oversight from the monitoring software SIMBA. We have found that within the CeA and Astr, there is large diversity in response types to unpaired cue, a footshock-paired cue, and reward delivery, as well as corresponding behavioral output. Over the course of the experiment, mice displayed extinction learning, which was then corresponded to a change in single-unit data. When compared to CS^-, there is a significant decrease in reward seeking during CS^+ and a significant increase in latency to resume reward seeking following CS^+ offset, however overall amount or reinforcers received does not change, indicating that the mice are compensating for this conditioned suppression at other points during the paradigm. Our findings replicate classic conditioned suppression studies, showing that a conditioned fear stimulus suppresses reward seeking behavior. Additionally, the electrophysiological data shows a diversity in responding that could indicate specific circuits to further study in association with valence processing and proper behavioral output. Future work will include identifying specific cell-types within the CeA and Astr to functionally manipulate in order to assess how valence processing and corresponding behavioral output are generated in the presence of stimuli with both positive and negative valences.

Disclosures: K. Anderson: None. **C.E. Stelly:** None. **J.P. Fadok:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.15/GG10

Topic: H.01. Fear and Aversive Learning and Memory

Support: R01MH118441, NIMH (EL)
PSY-CUNY Doctoral Student Research Grant (The Graduate Center) (TN)
Stanley Weiss Award in Experimental Psychology (MS)
T32GM156689, NIH (Hunter College, TN)

Title: Theta-to-gamma state transitions in the infralimbic cortex-basal forebrain circuit support fear extinction learning

Authors: *T. NABATIAN[1,3], C. FERNANDES HENRIQUES[1], G. LIFSHITS[3], M. SCLAR[3,2], E. LIKHTIK[1];
[1]Biol., [2]Pyschology, CUNY Grad. Ctr., New York, NY; [3]Biol., Hunter Col., New York, NY

Abstract: Extinction of fear memory is an adaptive process disrupted in stress and anxiety disorders. While infralimbic cortex (IL) projections to the basolateral amygdala (BLA) are critical for extinction memory consolidation, they are not required for extinction learning, suggesting IL engagement of other targets mediates learning. The basal forebrain (BF), involved in attention, BLA acetylcholine release, and associative fear learning, shares reciprocal connections with IL and BLA, positioning it to contribute to learning. Inhibiting IL-to-BF projections impairs extinction learning without affecting memory recall, suggesting IL-BF communication selectively supports learning. However, the circuit dynamics underlying this interaction remain unknown.

Using in-vivo local field potential recordings in IL and BF during extinction, we characterized oscillatory communication dynamics. Both regions showed cue-evoked increases in theta power (3-6Hz) during early extinction that returned to baseline by late extinction, while high gamma power (70-120Hz) showed the opposite pattern, indicating a shift from early theta-dominant to late gamma-dominant states. Early cue-evoked theta power correlated positively with extinction learning performance, whereas late gamma power predicted learning, suggesting these oscillations support distinct phases of learning. IL theta power led BF theta by ~8ms early, increasing to ~14ms late in extinction, indicating strengthened IL-to-BF theta communication across learning. Indeed, there was cue-evoked elevation in BF gamma power coupling to IL theta phase, suggesting IL organizes BF gamma during learning-relevant events. Furthermore, theta phase coherence between regions was elevated early but returned to baseline late, while gamma phase coherence showed the opposite pattern. When we related these changes to behavior across extinction, we found that theta phase coherence positively correlated with freezing, while gamma coherence negatively correlated with freezing, again demonstrating a theta-to-gamma shift as learning progresses.

Together, these findings support a model in which IL-BF circuit oscillatory states transition from early theta to late gamma as a signature of successful extinction learning. Given that IL projections preferentially target BF parvalbumin (PV) interneurons, key coordinators of gamma oscillations, we are using optogenetics to inhibit BF PV neurons during extinction to test their necessity for gamma emergence and learning. Further, we are probing whether IL-BF oscillatory dynamics are related to ACh release in the BLA, a key neuromodulator of memory formation in the amygdala.

Disclosures: T. Nabatian: None. **C. Fernandes Henriques:** None. **G. Lifshits:** None. **M. Sclar:** None. **E. Likhtik:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.16/GG11

Topic: H.01. Fear and Aversive Learning and Memory

Support: IN227123
IN217326

Title: Inhibition of cholinergic projections to the BLA during novel taste intake prevents attenuation of taste neophobia

Authors: *E. RODRÍGUEZ NAVA[1,2], R. ALCANTARA RIVAS[3], V. TORRES GARCÍA[4], J.-P. MORIN[5];
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Abstract: Background: The assignment of positive or negative valence to stimuli is essential for guiding adaptive approach and avoidance behaviors. One example is when an animal consumes an eatable with an unknown taste in small amounts The Basolateral Amygdala (BLA) is a critical hub for emotional learning and valence processing, which receives dense cholinergic innervation from Basal Forebrain nuclei (BF) cholinergic neurons. Although cholinergic signaling to the BLA has been implicated in emotional memory formation, its contribution to gustatory valence assignment remains poorly understood. Previous work from our laboratory showed that blockade of muscarinic receptors within the BLA of rats immediately following exposure to a novel taste (0.3% saccharin) promotes conditioned avoidance on test day, 48h later. However, because local muscarinic antagonism cannot identify the neuronal source of cholinergic signaling, we sought to determine whether cholinergic BF projections to the BLA were responsible for this effect. Methods: Heterozygous ChAT-IRES-Cre male mice were crossed with wildtype (WT) C57BL6J female mice to obtain ChAT-Cre and WT. Animals were infused retro-AAV-hSyn-DIO-hM4Di-mCherry bilaterally in the BLA. ChAT-IRES-Cre-expressing mice received clozapine-N-oxide (CNO) or vehicle 10 min before novel taste (0.5% saccharin; S1) under a two-bottle, taste/water choice paradigm and tested again 24 h later (S2). An additional group consisting of WT mice receiving CNO was included. The dependent variable was the preference index (PI; vol. sac./(vol. sac. + vol. water)*100). Results: Vehicle-injected ChAT-IRES-Cre-expressing mice and CNO-injected WT mice behaved similarly throughout the behavioral procedure and were therefore collapsed into a single control group. Two-way ANOVA unveiled a significant Day x Group effect ($F_{(1,4)}$=10.84, $p<0.05$). *Post hoc* analysis revealed that on S2, ChAT-IRES-Cre animals had a significantly lower PI compared to their WT littermates. Immunofluorescence analysis confirmed BF cholinergic origin, especially from the nucleus basalis magnocellularis and ventral pallidum. Discussion: Our findings suggest that chemogenic inhibition of cholinergic

inputs to the BLA after novel taste consumption reduces saccharin preference on subsequent exposure.

Disclosures: E. Rodríguez Nava: None. **R. Alcantara rivas:** None. **V. Torres García:** None. **J. Morin:** None.

Poster

PSTR322: Neural Circuits of Fear, Threat, and Defensive Behavior

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR322.17/GG12

Topic: H.01. Fear and Aversive Learning and Memory

Title: Noradrenergic control of reward and fear ensembles in mPFC

Authors: *E. L. BURKE[1], J. TAYLOR[3], A. P. KAYE[2];
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Abstract: Animals must adaptively seek rewards while avoiding threats, and dysregulation of these opposing motivational drives contributes to psychiatric disorders. Noradrenergic dysfunction has been implicated in both conditions, yet the precise computational role of NE in valence learning remains unknown. The medial prefrontal cortex (mPFC) has distinct neuronal populations encoding reward and fear, developing separable representations after learning. Norepinephrine (NE), released by the locus coeruleus (LC), has long been considered a generalized arousal signal that scales with stimulus salience regardless of valence. However, work from our lab and others has demonstrated that LC-NE neurons are functionally heterogeneous and that mPFC NE tracks threat association strength during fear conditioning, suggesting that NE may carry threat-specific rather than valence-general information. Prior studies have examined NE only during reward or threat learning in isolation, so it remains unclear whether mPFC NE represents a generalized arousal signal or a threat-biased teaching signal. I have created a dual reward-threat learning Pavlovian conditioning paradigm, in which 2 tones are presented to the animal, one being reward-predictive, and the other threat-predictive. Animals are able to successfully discriminate between these tones, as evident by divergent behavioral phenotypes (appetitive, reward-searching behavior exhibited during the CS_{reward} via magazine entry ($p=0.001$), and aversive/fearful, freezing behavior during the CS_{threat} ($p=0.016$). NE increases during the CS_{threat} significantly more than during the CSreward, suggesting that NE is involved in tracking threat more so than reward. In addition, optogenetically stimulating LC -> mPFC terminals during the CS_{threat} shows an increase in learning of discrimination between the two tones, as evidenced by the decreased magazine entry during the CS_{threat} than Cre- controls ($p=0.036$). Magazine entry times did not differ for the CS_{reward}, indicating that appetitive reward behavior was unchanged. On a single neuron level, using chronic Neuropixels recordings, I tracked neurons responding to the CSs and USs over the course of learning. I found that there were neurons that were specifically tuned to the CS_{reward}, CS_{threat}, or both CSs. Furthermore, a test

session was completed in which in which 1.0 mg/kg propranolol, a beta-adrenergic antagonist, was administered 10 minutes prior to the session. We found that CS_{threat} responsive neurons significantly decreased their response to the CS_{threat}, but not the CS_{reward}. Neurons tuned to CS_{reward} did not change their response to either CS_{reward} or CS_{threat}.

Disclosures: E.L. Burke: None. **J. Taylor:** None. **A.P. Kaye:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.01/GG13

Topic: H.01. Fear and Aversive Learning and Memory

Support: R01MH065961

Title: Theta-paced optogenetic stimulation of the thalamic nucleus reuniens attenuates contextual fear memory

Authors: *P. FANG[1,2], A. ARELLANO PEREZ[1], A. P. ABRAMENKO[1,2], T. TUNA[1], S. MAREN[1,2,3];
[1]Beckman Inst. for Advanced Sci. and Technol., Urbana, IL; [2]Neurosci. Program, [3]Psychology Dept., Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: The nucleus reuniens (RE) is a midline thalamic nucleus interconnecting the medial prefrontal cortex (mPFC) and the hippocampus (HPC). Recent work in our lab has revealed that theta oscillations (6-9 Hz) in the RE, HPC and mPFC are correlated with the suppression of conditioned freezing after auditory fear conditioning in rats. Moreover, theta-paced optogenetic stimulation of RE reduces the expression of fear to an auditory conditioned stimulus (CS) and facilitates extinction. Here we examined the effect of RE optostimulation on the expression of contextual fear conditioning in male and female rats. Prior to fear conditioning, animals received intra-RE infusions of adeno-associated viruses expressing either channelrhodopsin (ChR2; AAV9-hSyn-ChR2-mCherry) or control virus (AAV9-hSyn-mCherry). Three weeks after recovery from surgery, the animals were transported to a novel conditioning chamber where they received 5 footshocks (2 sec, 1 mA; 58s ISI) three minutes after placement in the chamber. Twenty-four hours later they were returned to the chambers for a 10 min test in which they received oscillatory optogenetic stimulation (8 Hz, 450 nm, 10 mW, 60 sec) either 0 or 3 min after placement in the chamber. The next day they received a second test in which stimulation delay (0 or 3 min) was counterbalanced in a within-subjects manner with the condition each rat experienced in the first test. We predicted that stimulation at either delay would be sufficient to disrupt the expression of contextual freezing. In contrast to this prediction, we observed that RE stimulation only suppressed fear expression in the delayed condition; freezing returned to control levels immediately after offset of the stimulation. The attenuation of freezing was not due to non-specific effects of the stimulation and appear to be due to a disruption in contextual memory

retrieval. These results reveal that theta-paced optostimulation of the RE regulates the expression of conditioned fear memories and may serve as basis for future therapeutic interventions.

Disclosures: P. Fang: None. **A. Arellano Perez:** None. **A.P. Abramenko:** None. **T. Tuna:** None. **S. Maren:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.02/GG14

Topic: H.01. Fear and Aversive Learning and Memory

Title: Cholinergic signaling in the basolateral amygdala regulates fear relapse

Authors: *F. MENCEVSKI[1], N. M. HOLMES[2], V. LAURENT[3];
[1]Sch. of Psychology, Univ. of New South Wales, Sydney, Australia; [2]Univ. of New South Wales, Sydney, Australia, Australia; [3]Psychology, UNSW Australia, Unsw Sydney, Australia

Abstract: Fear extinction inhibits rather than erases fear memories, as extinguished fear is renewed by shifts in physical contexts, spontaneously recovers with the passage of time and is reinstated following stressful events. This fear inhibition necessitates synaptic plasticity in the basolateral amygdala (BLA), which receives dense cholinergic inputs from the horizontal limb of the diagonal band of Broca (HDB). Recent work suggests that these HDB→BLA cholinergic projections regulate how extinction is learned and may control whether extinguished fear can renew, spontaneously recover or become reinstated. The present experiments aimed to confirm this suggestion and to provide insight into which cholinergic receptors regulate BLA activity during extinction. Using optogenetics in ChAT::Cre transgenic rats, we found that silencing the HDB→BLA cholinergic pathway during Pavlovian extinction abolished all restoration phenomena: extinguished fear no longer renewed, spontaneously recovered or reinstated. We then used BLA administration of the muscarinic antagonist scopolamine and/or the nicotinic antagonist mecamylamine to identify the receptors mediating this effect. Antagonising either receptor alone during extinction had no effect on subsequent renewal. By contrast, combined administration of both antagonists abolished renewal, indicating that muscarinic and nicotinic receptors act in concert to regulate BLA activity during extinction learning.

Disclosures: F. Mencevski: None. **N.M. Holmes:** None. **V. Laurent:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.03/GG15

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIAAA Intramural Research Program

Title: Investigating PFC representations in contextual fear discrimination using VR technology

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Abstract: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric illness characterized by abnormally persistent fear memories that are often triggered by context cues that bear similarity to those initially experienced during the incepting traumatic event. Contextual fear conditioning (CFC) can be used to measure an animal's ability to link environmental stimuli with an aversive experience, providing an avenue to investigate the neurobiology of PTSD. Studies using traditional CFC approaches suggest that the prefrontal cortex (PFC) may be a neural locus critical to the adaptive regulation of fear. While useful, traditional CFC paradigms have important limitations. For example, they require the physical transfer of animals between contexts across multiple days, which prevents the continuous measurement of neuronal activity across the distinct contexts. Additionally, PTSD can be triggered by instantaneous transitions from an innocuous context to one that triggers aversion, e.g., an individual with PTSD linked to battlefield trauma may be walking in an innocuous environment before an unexpected firecracker explosion induces a fear state. Such rapid context transitions are not captured by traditional CFC paradigms. Here, we implemented a virtual reality (VR) CFC paradigm to address these limitations. Mice were placed in a cylindrical apparatus lined with LEDs that could be nearly instantaneously changed from one context to another. Mice were able to discriminate on a moment-by-moment basis between an aversive context (paired with footshock) and a neutral context (no footshocks). To demonstrate the necessity of PFC to fear discrimination, we chemogenetically inhibited PFC neurons during a discrimination session where contexts transitioned from aversive to safe. Chemogenetic inhibition of PFC resulted in elevated fear, as compared to controls. Finally, we recorded the activity of PFC neurons using 1-photon microendoscopic calcium imaging, demonstrating that neurons are sensitive to aversive stimuli and provide contextual information. Ongoing experiments are identifying circuit mechanisms relevant to the cortical control of rapid contextual fear.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.04/GG16

Topic: H.01. Fear and Aversive Learning and Memory

Support: Israel Science Foundation
U.S.- Israel Binational Science Foundation

Title: Regulation of Fear Memory by Intersectin-1 at Prefrontal Cortex Synapses in the Basolateral Amygdala

Authors: *A. FARHAT[1], S. BHOWMICK[1], M. ATTIAS[1], R. LAMPRECHT[2];
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Abstract: Intersectin-1 (ITSN1) is a multidomain scaffolding protein that functions as a guanine nucleotide exchange factor (GEF) for Cdc42. To enable optical control of ITSN1 activity, we used a photoactivatable ITSN1 construct (PA-ITSN1). We then investigated the role of ITSN1 in fear memory using the PA-ITSN1 to achieve precise temporal and spatial control of ITSN1 GEF activity at prefrontal cortex (PFC) projections to the basolateral amygdala (BLA). Using auditory fear conditioning, we examined whether activation of PA-ITSN1 at PFC-BLA synapses influences fear memory. Activation of PA-ITSN1 24 hours after fear conditioning enhanced long-term fear memory. This enhancement was not accompanied by changes in synapse number within the BLA but required synaptic transmission from PFC terminals in the BLA. In contrast, activation of PA-ITSN1 in BLA neurons 24 hours after fear conditioning did not affect long-term fear memory. These findings identify ITSN1 as a regulator of fear memory at PFC-BLA synapses and demonstrate that activation of ITSN1 GEF activity in this pathway is sufficient to enhance long-term fear memory.

Disclosures: A. Farhat: None. **S. Bhowmick:** None. **M. Attias:** None. **R. Lamprecht:** None.

Poster

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Program #/Poster #: PSTR323.05/GG17

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH MH122414

Title: Reductions in the monoubiquitination of histone H2B in the retrosplenial cortex are a critical regulator of fear memory formation

Authors: *H. VENKAT[1,9], K. CURRIER[2,10], M. TURNER[3], N. ZINCONE[4], S. HILL[5], O. BALL[6], J. HERMANSON[7], A. JAROME[8], T. J. JAROME[3];
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Abstract: The formation of long-term memories requires dynamic changes in gene transcription. Post-translational modifications of histone proteins are potent epigenetic mechanisms that regulate gene transcription underlying memory formation. Histone monoubiquitination, in which ubiquitin attaches to histone proteins at specific lysine residues, can bidirectionally regulate gene transcription depending on which histone protein is modified. Previous work from our lab revealed a critical role for the monoubiquitination of histone H2B (H2Bubi) as a master regulator of active and repressive gene transcription during contextual fear memory formation in the hippocampus. However, the role of H2Bubi in memory formation in brain regions outside the hippocampus remains unclear. The retrosplenial cortex (RSC) is an interconnected brain region involved in spatial navigation, learning, and episodic memory, yet remains poorly understood despite its implication in age-related memory decline and neurological disorders that present with memory impairments. Here, we examined the role of H2Bubi in the RSC during the consolidation of a contextual fear memory. We found significant decreases in H2Bubi levels in the RSC of young adult male rats following contextual fear conditioning. Further experiments demonstrated that these reductions in H2Bubi in the RSC were driven by exposure to the training context or footshock when presented in a non-associative manner, suggesting that the RSC may be responding to different sensory components of the training experiment rather than direct involvement in associating these cues. In vivo CRISPR-dCas9-VPR-mediated upregulation of the only ubiquitin E3 ligase for H2B, Rnf20, in the RSC significantly impaired contextual fear memory. Together, our findings reveal that learning-induced reductions in H2Bubi in the RSC are a critical regulator of contextual fear memory formation. These results advance our understanding of the molecular and epigenetic mechanisms that support memory formation.

Disclosures: H. Venkat: None. **K. Currier:** None. **M. Turner:** None. **N. Zincone:** None. **S. Hill:** None. **O. Ball:** None. **J. Hermanson:** None. **A. Jarome:** None. **T.J. Jarome:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.06/GG18

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH MH122414

Title: Asymptomatic infection with La Crosse Virus or Jamestown Canyon Virus leads to lasting reductions in motivation and exploratory behavior in mice

Authors: *T. J. JAROME[1], B. BROWN[2], M. TURNER[1], J. HERMANSON[1], A. JAROME[1], O. BALL[1], M. GOSAI[2], S. PAULSON[3], A. GROSS[3];
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Abstract: The United States is experiencing a rise in mental health issues, with anxiety disorders being the most prevalent. In 2022, approximately 19.1% of adults reported experiencing an anxiety disorder, and this prevalence tends to be significantly higher among individuals residing in rural areas where mosquito populations are abundant. However, there remains limited information on the causal relationship between neurotropic arthropod-borne viruses (arboviruses) endemic to the U.S. and the increase in anxiety disorders. La Crosse Virus (LACV) is an arbovirus endemic in the U.S. that can cause severe neuroinvasive disease in children. Conversely, Jamestown Canyon Virus (JCV), which is also endemic to the U.S., primarily affects adults. Most LACV and JCV infections across all ages are either asymptomatic or cause mild symptoms that are typically not reported. Currently, it is unknown whether prior asymptomatic infections with arboviruses, such as LACV and JCV, can lead to lasting behavioral changes. Here, 4-week-old pediatric male mice received intraperitoneal injections of low-titer LACV or JCV, resulting in asymptomatic infection. Thirty days later, these mice were tested on two behavioral tasks to assess anxiety-like and exploratory behaviors. Relative to control-injected mice, LACV-infected mice did not show changes in time spent in the open arm of the elevated plus maze, nor in entries into the open and closed arms of the maze. However, LACV-infected mice had reduced time exploring the center of the open field apparatus and less total grid crossing, indicating reduced motivation and exploratory behavior relative to control animals. Interestingly, we observed significant reductions in total grid crossings but not time in the center of the arena in mice asymptomatically infected with JCV, suggesting general hypoactivity and reduced motivation. Together, these data suggest that prior asymptomatic infection with LACV and JCV in children could lead to lasting changes in motivation and exploratory behavior in young adulthood, which are potential signs of increased anxiety. Current experiments are examining how prior LACV and JCV infection impacts biological processes in the amygdala, the primary brain region involved in fear, anxiety, emotion, and motivation.

Disclosures: T.J. Jarome: None. **B. Brown:** None. **M. Turner:** None. **J. Hermanson:** None. **A. Jarome:** None. **O. Ball:** None. **M. Gosai:** None. **S. Paulson:** None. **A. Gross:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

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Program #/Poster #: PSTR323.07/GG19

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH grant MH122414

Title: Protein SUMOylation in the retrosplenial cortex is involved in fear memory formation in a sex-dependent manner

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Abstract: Over the last three decades, strong evidence has emerged implicating a role for protein ubiquitination in memory formation. Less studied, though, is protein SUMOylation, a process that competes with ubiquitin and promotes protein stability, cellular localization, and protein-protein interactions. Recently, it has been shown that protein SUMOylation is critically involved in memory formation in the hippocampus and amygdala (e.g., Gustin et al. 2022) and is an important regulator of post- and pre-synaptic signaling throughout the brain of both sexes (Schorova & Martin 2016). The retrosplenial cortex (RSC) is thought to aid in the hippocampal-amygdalar system when forming contextual fear memories, and we have recently shown that learning-induced repression of protein degradation by the ubiquitin-proteasome system (UPS) in the RSC is critical for the formation of contextual fear memories in both sexes (Turner et al. 2026). However, whether SUMOylation is involved in contextual fear memory formation in the RSC has yet to be examined. In this study, using unbiased SUMO-specific proteomics, we found sex-specific changes in SUMOylation in the RSC following contextual fear conditioning. In the female RSC, SUMOylation increased or decreased at 76 and 19 proteins, respectively, following fear conditioning. Contrary to the large number of targets in females, males had 8 proteins with significantly altered SUMOylation, 5 of which have decreased levels. Interestingly, in females, SUMOylation was preferentially increased at proteins involved in GABA signaling, potentially indicating a role of SUMOylation in the regulation of inhibitory signaling. Conversely, in males, SUMOylation protein targets were mainly involved in mitochondrial protein dysfunction and keratinization. Despite these sex differences in SUMOylation targets, siRNA-mediated knockdown of *Ube2i*, the enzyme that conjugates all SUMOylation in cells, in the RSC enhanced contextual fear memory retention in a mixed sex cohort. Together, these data reveal a novel, sex-specific role for protein SUMOylation in the RSC during the formation of a contextual fear memory.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

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Program #/Poster #: PSTR323.08/GG20

Topic: H.01. Fear and Aversive Learning and Memory

Support: MH117791

Title: Dorsomedial striatum firing dynamics during concurrent fear conditioning and active avoidance

Authors: *T. B. MAZONSON, N. T. GORDON, L. H. COUNSMAN, M. MOADDAB, M. A. MCDANNALD;
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Abstract: Environmental threats present themselves in many ways. Some threats are avoidable; a deft action will prevent harm. Others are inevitable and cannot be stopped, only prepared for. Adaptive behavior requires animals to learn not only which events are threatening, but also whether a given threat can be controlled through action. In a laboratory setting, avoidable threats can be studied with avoidance learning, and inevitable threats with Pavlovian fear conditioning. Emerging evidence identifies the dorsomedial striatum as a key brain region for detecting the relationship between an action and the omission of an aversive event, a defining feature of negative reinforcement. However, the dorsomedial striatum may also play a more general role in threat detection or in coordinating an 'active' fear response. The goal of this experiment was to determine whether the dorsomedial striatum functions as a key neural substrate for negative reinforcement: detecting the action-omission relationship. We developed a novel procedure in which rats underwent concurrent avoidance learning and fear conditioning. First, all rats underwent 5 days of pretraining. At all times, rats were able to nose poke for a food reward at the front of the chamber. Intermittently, three distinct 20-s auditory cues were presented: a danger cue always preceded mild foot shock, a neutral cue was never paired with foot shock, and an avoidance cue preceded foot shock unless movement to the rear of the chamber was made. If this movement was executed, the tone ceased, and foot shock was omitted. Rewarded nose poking was not contingent upon cue presentation or footshock delivery. After pretraining, Long-Evans rats (n = 13, 7 females) were implanted unilaterally with a drivable micro-electrode bundle dorsal to the dorsomedial striatum (AP: -0.24, ML: -2.2, DV: -2.4). Following recovery, we recorded single-unit activity while rats underwent the concurrent avoidance and fear conditioning paradigm. We recorded over 300 single units from over 125 behavior sessions. During these sessions, rats demonstrated behavioral discrimination of the avoidance, danger, and neutral cues. Both avoidance and danger cues suppressed rewarded nose poking at the front of the chamber. It is possible that the movement to the rear of the chamber elicited by both cues was likely to be driven by different underlying motivations. Individual dorsomedial striatum neurons showed differential firing based on avoidance success and behavioral responses. A complete analysis of dorsomedial striatum firing with respect to avoidance behaviors during discriminative sessions will be presented.

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Poster

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Program #/Poster #: PSTR323.09/GG21

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant MH117791

Title: The periaqueductal gray is necessary for conditioned freezing but dispensable for unconditioned stimulus inflation

Authors: *L. H. COUNSMAN, G. E. VALVO, C. F. LAMBERSON, A. M. DUBOIS, Z. V. LYU, H. E. KIM, T. S. LEE, M. J. GARCIA-VIESCA, J. B. BOYCE, S. M. SHEN, A. C. FITZPATRICK, M. L. DAVID, M. MOADDAB, M. A. MCDANNALD;
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Abstract: Adaptive behavior requires animals to make threat predictions, and update those predictions in light of new information. In turn, these updated predictions must be utilized to calibrate fear responding. The periaqueductal gray is traditionally viewed as a downstream structure to organize fear responding, specifically through freezing. Experiment 1 tested whether the periaqueductal gray is necessary for US inflation of fear responding. We deleted neurons across the complete anterior-posterior span of the periaqueductal gray using a dual-viral approach, then quantified deletion extent and subregion specificity using machine-learning methods. Control and deleted rats completed a novel US inflation procedure, assessing both inferred and direct fear inflation. Periaqueductal neuronal deletion reduced overall fear responding as well as freezing, but left both inferred and direct inflation intact. This means that periaqueductal deletions that diminished freezing had no impact on updating threat predictions through inflation. To address this, Experiment 2 saw control and deleted rats receive discrimination in which a threat cue predicted foot shock with 30% or 10% probability, while a neutral cue never predicted foot shock. Control rats showed probability-dependent scaling of fear responding (threat > neutral, and 30% > 10%), which was abolished by periaqueductal gray neuronal deletion (threat > neutral, but 30% ≈ 10%). The total results show that the capacity to form and update threat predictions, as well as their underlying neural circuits, are distinct from circuits for freezing. The results further show that periaqueductal gray function depends on the threat situation. Minimal threat settings see the periaqueductal gray aligning total fear responding to probability while intense threat settings see the periaqueductal gray organizing freezing.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

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Topic: H.01. Fear and Aversive Learning and Memory

Support: NSERC Grant RGPIN-2018-04401
CIHR Grant #PJT-169197

Title: Astrocytic Adrenergic Signaling in the Basolateral Amygdala During Second-Order Threat Conditioning

Authors: *T. SEPAHVAND, K. POWER, N. NAZARI, T. QIN, T. SIDDIQUI, Q. YUAN; Fac. of Med., Mem. Univ. of Newfoundland, St. John's, NL, Canada

Abstract: Second-order conditioning (SOC) enables indirect associations between neutral sensory cues and threats beyond first-order conditioning (FOC). This higher-order associative process is particularly relevant to post-traumatic stress disorder (PTSD), wherein multiple layers of associations may develop around the original traumatic event. We established an auditory-olfactory SOC paradigm in rats to investigate neural mechanisms underlying higher-order threat learning. Neuromodulatory input from the locus coeruleus (LC) is essential for affective learning, particularly in the basolateral amygdala (BLA), a hub for threat learning. Astrocytes have also emerged as active contributors to synaptic plasticity and memory processes. Here, we investigated the contribution of LC signaling and astrocytic versus neuronal adrenergic receptors in the BLA during SOC. First, LC neurons were chemogenetically silenced using a Cre-dependent inhibitory Designer Receptor Exclusively Activated by Designer Drug (DREADD), selectively expressed in the LC of male TH-Cre rats via viral vector infusion. The DREADD ligand Deschloroclozapine (DCZ) was administered systemically to activate inhibitory signaling. Control animals received adeno-associated virus expressing green fluorescent protein (AAV-GFP). LC silencing during SOC acquisition significantly impaired SOC memory, indicating that LC activity is required for the acquisition of higher-order threat memory. Silencing the LC during SOC retrieval produced a trend toward impaired retrieval ($p = 0.096$). Next, adrenergic receptor signaling in the BLA was manipulated using cell-type-specific AAV knockdown constructs targeting β2-adrenergic receptors in either neurons or astrocytes. Viruses were infused into the BLA of male Sprague-Dawley rats; AAV-GFP served as a control. β2-adrenergic receptor knockdown in neurons did not affect SOC retrieval or one-week memory retention, whereas astrocytic β2 receptor knockdown impaired SOC retrieval, suggesting a role for astrocytic β2 signaling in the expression of second-order threat memory. Ongoing work investigates α1- and β1-adrenergic receptors in astrocytes and neurons within the BLA to further define how LC neuromodulation regulates higher-order threat learning. These results provide insight into circuit and cellular mechanisms underlying complex associative threat processes relevant to PTSD.

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Poster

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Topic: H.01. Fear and Aversive Learning and Memory

Support: DSI-MnDRIVE PhD Graduate Assistantship

Title: Characterizing Mesoscale Cortical Dynamics during Fear Conditioning and Extinction in Mice

Authors: *M. R. LEHMAN[1], K. SAXENA[2], D. A. SURINACH[3], S. B. KODANDARAMAIAH[4], I. OLADEPO[5];
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Abstract: The dorsal cerebral cortex contains many subregions which are implicated in sensory processing and the generation of motor plans and actions. In this study, we seek to understand how fear, a defensive survival state in mice, changes spatiotemporal activity in the cerebral cortex. We used a head-mounted microscope to image pan-cortical calcium activity in GCaMP6f mice undergoing Pavlovian fear-conditioning. On the first day, an experimental group of mice (n=8) was habituated to a 5kHz auditory tone, serving as the conditioned stimulus (CS), and subsequently subjected to five coterminous pairings with a 0.6mA 0.5s footshock, serving as an unconditioned stimulus (US). A control group (n=5) received exposure to the same CS and US in a pseudorandom unpaired fashion, limiting CS-US association. On a second and third testing day, both the control and experimental group were exposed to ten CS presentations to test for fear and extinction learning. Learning was measured using manually scored instances of freezing among both groups. Imaged brain data were input to a machine learning model that performs dimensionality reduction using K-means clustering. This method sorts all frames of cortical activity from a video into K clusters of the most common spatial expressions, which we call “temporary cortical states”. K is selected such that these temporary states accurately reconstruct the original video. To identify how internal state changes cortical activity, we use a simple probability model to stereotype sequences of temporary states that occur during freezing behaviors. In our conditioned group, we found two primary changes. First, conditioned mice demonstrated a posterior-dominated temporary state prior to the onset of a freezing event. Conversely, control mice demonstrate a different medioanterior sequence only after freezing occurs. Second, cortical activity in conditioned mice progresses from posterior to medioanterior activity over increasingly longer timescales during extinction, while controls exhibit the same sequences over the same timescales across all days. The results of the K-means model are confirmed by analysis of activity averaged from regions of the cerebral cortex, and indicate a unique recruitment of cortical regions associated with fear.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

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Topic: H.01. Fear and Aversive Learning and Memory

Support: FAPESP 2022/02986-0
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FAPESP 2025/06416-1
CAPES-PROEX 001

Title: Systemic but not ventral tegmental area corticosteroid signaling modulates elevated plus maze behavior in male and female rats

Authors: *L. M. TAGUCHI[1], P. TIMOSSI[2], C. DE OLIVEIRA ALVES[2], A. R. DE OLIVEIRA[3];
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Abstract: Corticosterone regulates diverse components of the rodent stress response, and its release can be triggered by both conditioned and unconditioned aversive stimuli. Corticosteroids act via two receptor types: mineralocorticoid (MR) and glucocorticoid (GR) receptors. While MR antagonism in the ventral tegmental area (VTA) reduces conditioned fear in male rats, its role in unconditioned fear remains poor understood. This study investigates the role of systemic corticosterone synthesis inhibition versus intra-VTA MR and GR blockade on unconditioned defensive behaviors in the elevated plus maze (EPM) in both male and female rats. Adult Wistar rats (99 males, 150 females; CEUA 3078260423 and 2425060423) were evaluated across three experimental designs. Experiment 1 evaluated systemic corticosterone synthesis inhibition via intraperitoneal metyrapone (0, 30, or 60 mg/kg). Experiments 2 and 3 assessed local intra-VTA microinjections of the MR (spironolactone) or GR (mifepristone) antagonists (0, 5, or 10 ng/0.2 μL). Animals were tested in the EPM for 5 min, and behavioral parameters were recorded. Data were analyzed using one-way ANOVAs followed by Tukey's post hoc tests ($p < 0.05$). Systemic metyrapone at 60 mg/kg (Mety60) significantly increased open-arm entries in both males ($F_{2,35} = 3.92$, $p < 0.05$) and females ($F_{2,71} = 3.50$, $p < 0.05$). No such effect was found following intra-VTA MR (males: $F_{2,37} = 0.30$, $p > 0.05$; females: $F_{2,49} = 3.03$, $p = 0.057$) or GR (males: $F_{2,18} = 0.95$, $p > 0.05$; females: $F_{2,21} = 1.28$, $p > 0.05$) antagonism. Closed-arms entries were significantly decreased by Mety60 (males: $F_{2,35} = 3.57$, $p < 0.05$; females: $F_{2,71} = 15.30$, $p < 0.05$), with no significant effect for MR (males: $F_{2,37} = 1.79$, $p > 0.05$; females: $F_{2,49} = 0.33$, $p > 0.05$) or GR (males: $F_{2,18} = 2.55$, $p > 0.05$; females: $F_{2,21} = 1.01$, $p > 0.05$) antagonists. Vertical exploration (rearings) was significantly reduced by Mety60 (males: $F_{2,35} = 6.43$, $p < 0.05$; females: $F_{2,71} = 21.23$, $p < 0.05$) and by intra-VTA mifepristone at 5 ng/0.2 μL in males ($F_{2,18} = 4.19$, $p < 0.05$). No significant differences were detected for time spent in the open arms, head dips, or open-arm end exploration ($p > 0.05$). These findings demonstrate that systemic corticosterone synthesis inhibition exerts an anti-aversive effect, increasing open-arm entries while reducing general exploratory behavior (rearings and closed-arm entries) in both sexes. While intra-VTA GR blockade selectively reduced rearing in males, the overall lack of

robust EPM changes following intra-VTA administrations suggests that corticosterone modulates unconditioned fear primarily through neural circuits outside the VTA.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

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Program #/Poster #: PSTR323.13/GG24

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH Grant R00MH119320

Title: Interneuron-Mediated Activity in the PL as a Mechanism of Fear Acquisition in Adults and Adolescents

Authors: *B. BLOCKER[1], R. A. SENNE[1], H. C. MEYER[2], D. AL HUMAIDI[2];
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Abstract: Appropriate affective responses to fear and safe stimuli are adaptive traits that engage the inhibitory circuitry of the prelimbic prefrontal cortex (PL). However, the exact inhibitory mechanisms driving these affective responses are not fully known. Further, adolescence is marked by increased neural plasticity and dynamic changes in connectivity within the prefrontal inhibitory circuit, which renders this age group incredibly vulnerable to fear-related disorders. To better understand how inhibitory circuitry influences fear regulation, and whether this differs between adolescents and adults, we studied the role of parvalbumin (PVIs) and somatostatin (SSTIs) interneurons in fear and safety learning. We first observed PVI activity in male or female, adult or adolescent, PV-Cre mice that underwent four days of discriminative conditioning, which consisted of two 20-second fear tones co-terminating with a footshock and 28 safety tones (no shock). On the fifth day, mice were tested in a novel context using a summation test, in which 3 fear, 3 safety, and 3 compound tones (fear and safety tones presented simultaneously) were delivered (in later groups, 6 of each tone were delivered). Fiber photometry recordings were obtained during all behavioral sessions. During discrimination training, PVI activity at fear-tone onset increased across learning days in both adults and adolescents, a pattern specific to the fear tone and absent during safety-tone presentations. During the summation test, PVI tone-onset and tone-offset responses followed a consistent pattern across both age groups: fear tones elicited the largest peak response, safety tones the smallest (except no activity was observed during safety offset), and compound tones fell in between. A separate cohort of adult female and male SST-Cre mice underwent the same protocol. Across discrimination days, SSTIs also showed increased activity to the fear tone, with this activity sustained throughout the 20 seconds and increasing in magnitude over the 4 days. During the summation test, SSTIs show very small onset activity for the fear and compound

tones and little offset activity. Overall, this data shows that PVIs and SSTIs respond notably to fearful stimuli in the PL, driving both the learning and signaling of fear.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.14/HH1

Topic: H.01. Fear and Aversive Learning and Memory

Title: Real Time Virtual Reality Operant Conditioning Reveals Impaired Reinforcement Learning Following Entopeduncular-Habenular Circuit Ablation in Adult Zebrafish

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Abstract: Operant reinforcement learning depends on neural circuits capable of integrating behavioral output with sensory feedback and outcome evaluation. The ventral habenula is implicated in aversive processing and behavioral adaptation across vertebrate species, though the contribution of specific afferent pathways to reinforcement learning remains incompletely understood. In the present study, adult zebrafish were used to investigate the role of the entopeduncular-ventral habenula (EP-vHb) pathway during closed-loop operant conditioning. Individual fish were first assessed for baseline directional preference within a custom virtual reality arena and were subsequently trained against this intrinsic turning bias using a reinforcement paradigm in which visual stimuli changed dynamically according to ongoing locomotor behavior. Swimming in the target direction triggered presentation of a rewarding schooling zebrafish stimulus, whereas swimming in the default direction triggered presentation of an aversive Indian bullfrog stimulus. Real-time locomotor tracking was performed using DLC-Live based pose estimation. Selective disruption of the EP-vHb pathway was achieved using a y471;14xUAS epNTR-TagRFP transgenic line combined with metronidazole-mediated nitroreductase ablation. Control zebrafish displayed progressive acquisition of reinforced directional switching behavior and demonstrated significantly elevated target-directed performance relative to baseline expectations ($p = 0.0078$). In contrast, ablated animals exhibited a significantly reduced learning success rate compared with controls (12.5% vs. 71.4%; Fisher's exact test, $p = 0.0406$) and showed a trend toward lower peak reinforcement performance (45.1% vs. 74.6%; one-tailed Welch's t-test, $p = 0.052$). These findings support a role for the EP-vHb pathway in adaptive reinforcement learning and demonstrate the utility of closed-loop virtual reality paradigms for investigating neural circuit function in adult zebrafish.

Disclosures: C. Alrawashdeh: None. **J.S. Kanwal:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.15/HH2

Topic: H.01. Fear and Aversive Learning and Memory

Support: This work was supported by the NIH (R01 MH119283)
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Title: Noradrenergic Recruitment of CCK Interneurons Shapes Amygdala Network Dynamics and Fear Memory Formation

Authors: *G. P. SHELKAR[1], X. FU[3], E. COLEMAN[4], P. ANTONOUDIOU[5], J. MAGUIRE[5], J. G. TASKER[2];
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Abstract: The basolateral amygdala (BLA) is a critical neural hub for the integration of emotional information, fear processing, and emotional memory formation. Among the neuromodulatory systems that regulate BLA function, noradrenergic signaling exerts a profound influence on neuronal excitability, synaptic plasticity, and network activity. Norepinephrine released from locus coeruleus projections acts through α_1-, α_2, and β-adrenergic receptors to modulate BLA circuits; however, the cell type-specific mechanisms by which noradrenergic signaling regulates fear-related network activity remain poorly understood. In particular, the noradrenergic neuromodulatory regulation of cholecystokinin (CCK)-expressing inhibitory interneurons in the BLA has not been established. Here, we demonstrate that CCK basket cells are selectively activated by Gq-coupled α1A-adrenergic receptors to generate rhythmic inhibitory synaptic output onto BLA principal neurons that shapes local network states. Using an interneuron-specific viral strategy, we selectively expressed α1A-adrenergic receptors or a Gq-coupled DREADD in BLA CCK interneurons of global Adra1A knockout mice. Restoration of α1A receptor- or introduction of DREADD-mediated Gq signaling rescued rhythmic inhibitory synaptic activity and significantly enhanced theta- and suppressed gamma-frequency oscillations in the BLA in acute brain slices and in vivo. Importantly, selective rescue of α1A receptor signaling or activation of Gq-DREADD in CCK interneurons reduced fear memory acquisition and recall, indicating a critical role for this circuit in regulating fear learning. These results reveal a previously unrecognized inhibitory mechanism whereby Gq-coupled receptor activation in CCK interneurons promotes patterned inhibition that shapes BLA network oscillations to constrain fear memory formation, revealing a G protein-dependent neuromodulatory mechanism that regulates network oscillations, emotional state, and amygdala function.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.16/HH3

Topic: H.01. Fear and Aversive Learning and Memory

Support: MH117791

Title: Representing avoidable and inevitable threats in rodent prelimbic cortex

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Abstract: Detecting and responding to threats is vital to survival. However, not all threats are created equal. Some are inevitable; because we cannot stop them, all we can do is prepare. Other threats are avoidable, given an appropriate response. It is critical that an animal is able to both identify the presence as well as properties of a threat in order to organize an adaptive behavioral response. Failure to do so is a key feature of anxiety and stress disorders, where individuals may misinterpret benign stimuli as threats while simultaneously struggling to mobilize an effective reaction. Traditionally, inevitable threats are studied in the laboratory with Pavlovian conditioning. Avoidable threats are studied with avoidance learning, in which the animal is similarly presented with a threat cue, but can prevent the shock by performing some action. The goal of this experiment was to reveal prelimbic representations of avoidable and inevitable threats. To do this we developed a novel procedure in which single rats undergo concurrent avoidance learning and fear conditioning. At all times, rats nose poke for food in the front of the chamber. Intermittently, one of three 20s cues was presented; a danger cue that always predicts foot shock, a neutral cue that never predicts foot shock, and an avoidance cue predicts foot shock unless a movement to the chamber rear is made. If this movement is made, the cue ceases to play, and shock is omitted. Long Evans rats (n= 13, 10 female) were minimally pre-trained on the procedure, then unilaterally implanted with drivable micro-electrodes targeting the prelimbic cortex (AP: 2.7 / 2.5; ML: -.5; DV: -1.8 / -2.0 for females and males respectively). 250+ prelimbic single units were recorded from 150+ behavior sessions. During these sessions, rats showed complete behavioral discrimination of the avoidance, danger, and neutral cue. Both the danger and avoidance cues suppressed reward seeking at the chamber front, though differently. Further, both threat cue types promoted movements to the chamber rear, though again differently. Individual prelimbic cortex neurons show differential firing based cue presentation and shock omission. A complete analysis of behavioral responding and prelimbic firing dynamics will be presented.

Disclosures: N.T. Gordon: None. **M. Moaddab:** None. **T.B. Mazonson:** None. **L. Counsman:** None. **M.A. McDannald:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.17/HH4

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIDA Intramural Research Program
NIH Center on Compulsive Behaviors postdoctoral fellowship to MCB

Title: Nucleus accumbens representation of reward and punishment learning

Authors: *M. C. BROOMER, G. KUMAR, C. CLARK, G. BARBERA, D.-T. LIN;
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Abstract: Reward-seeking behavior is associated with activity in D1 and D2 receptor-expressing neurons in the nucleus accumbens (NAc). This activity tracks response initiation and reward consumption as well as the expectation of reward and how that expectation is updated following reward delivery or omission. However, it is unclear how these neurons encode new inhibitory learning when contingencies change and an animal must alter its behavior. We used miniscopes to record activity from D1- and D2-expressing NAc core neurons in male and female D1- and D2-Cre rats and applied machine learning-assisted analyses to characterize behavioral changes during context-dependent punishment learning and subsequent context-induced reinstatement. Rats were trained to lever press for food reward in Context A, then were punished for doing so in Context B. Punished responses earned a brief footshock set to 0 mA for two baseline sessions and increased 0.1 mA per session until animals stopped lever pressing. Finally, rats received a test session in each context to assess context-induced reinstatement of the punished response. All rats exhibited successful punishment-induced response suppression and context-induced reinstatement. Analysis of three-dimensional pose tracking data characterized longitudinal changes in task engagement, indecisiveness, and behavioral disorganization, and revealed pronounced changes in engagement and indecisiveness upon introduction of high-intensity punishment. Behavioral disorganization, a composite measure of spatial and transitional entropy, increased steadily across punishment. Behavioral changes were underscored by changing patterns of neural activation across punishment. Principal components analysis of population-level activity during four different response types—those that earned reward, punishment, both, or neither—revealed shifting neural representations of outcome configurations over the course of punishment. Early in punishment, different configurations elicited similar patterns of neural activity. These patterns diverged over the course of punishment, with the greatest difference emerging between responses that earned both outcomes vs. those that earned neither. A similar trend immediately preceding the response suggested that neural activity tracked the expectation of outcomes. These results characterize subtle behavioral changes throughout punishment learning and suggest that these changes may be associated with changing neural representations of appetitive and aversive outcomes.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.18/HH5

Topic: H.01. Fear and Aversive Learning and Memory

Support: IN227123
IN217326
1159410

Title: Muscarinic signaling in the basolateral amygdala gates post-experience valence assignment

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Abstract: Muscarinic signaling in the basolateral amygdala gates post-experience valence assignmentVíctor Manuel Torres García[1], Emmanuel Rodríguez Nava[1,2], Rosa Itzel Alcantara Rivas[1], Jean-Pascal Morin[1,✉][1]Department of Physiology, Faculty of Medicine, National Autonomous University of Mexico (UNAM). [2]Section of Postgraduate Studies and Research, School of Medicine, National Polytechnic Institute.[✉]Corresponding author: Dr. Jean-Pascal Morin, Department of Physiology, Faculty of Medicine, UNAM, Universidad 3000, Ciudad Universitaria, Coyoacán 04510, Mexico City, Mexico. Email: jpmorin@comunidad.unam.mx
The ability to assign emotional value, or valence, to experience is essential for adaptive behavior and survival. However, the mechanisms through which emotional value becomes incorporated into memory representations remain poorly understood. Traditionally associated with attention and memory consolidation, cholinergic neurotransmission within limbic circuits has increasingly been implicated in emotional learning. We recently demonstrated that muscarinic receptor antagonism within the basolateral amygdala of rats immediately following consumption of a palatable taste induces conditioned avoidance of that taste during subsequent encounters. In the present study, we report similar effects following systemic administration of the muscarinic antagonist scopolamine and demonstrate that muscarinic signaling within the BLA is both necessary and sufficient for this phenomenon. Using high-resolution licking microstructure analysis, we further identify a behavioral signature of scopolamine-induced avoidance that is clearly distinguishable from classical lithium chloride-induced conditioned taste aversion and is associated with a downward shift in established behavioral indices of taste valence. Finally, neural activity mapping revealed that scopolamine-induced avoidance reproduces key features of

the neural activation pattern previously described for lithium chloride-induced conditioned taste aversion while also generating a distinct pattern of activity not observed following malaise-based learning. Together, these findings identify BLA muscarinic signaling as a critical regulator of emotional valence assignment and reveal that disruption of this signaling is sufficient to induce maladaptive avoidance of an otherwise appetitive stimulus.

Disclosures: V. Torres García: None. **E. Rodríguez Nava:** None. **R. Alcantara rivas:** None. **J. Morin:** None.

Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.19/HH6

Topic: H.01. Fear and Aversive Learning and Memory

Support: S21MD001830
NIMHD U54 MD00760
COBRE P30 GM149367

Title: Antibiotic exposure contributes to persistent avoidance via dysregulation of activity in the ventral striatum in rats

Authors: N. M. JIMENEZ-RIVERA[1], L. L. MENDEZ-SANTACRUZ[3], H. HADDOCK-MARTÍNEZ[1], O. MARTÍNEZ GUZMAN[2], *D. SIERRA-MERCADO[1];
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Abstract: BACKGROUND: Converging lines of evidence, in addition to our preliminary data, demonstrate that antibiotic exposure increases anxiety-like behaviors in rodents. Of note, increases in anxiety may exacerbate other defensive behaviors, such as avoidance. However, the influence of antibiotics on avoidance, is largely unexplored.
METHODS: Avoidance can be tested in rats using platform-mediated avoidance. Here, a conflict is created that requires a choice between avoidance of a mild footshock and reward seeking of sucrose pellets. To achieve this, rats are trained to avoid the shock by stepping onto an acrylic platform during presentation of a conditioned auditory tone (30 sec, 4 khz, 78 dB, 3 min I.T.I.). Stepping onto the platform protects the rat from the shock, but does not eliminate the auditory stimulus. Moreover, the rat is unable to access the reward when it is on the platform. Given that antibiotic exposure increases anxiety, we hypothesized that antibiotics would result in persistent avoidance. To test this idea, adult male Sprague-Dawley rats were trained for 9 trials per day over 10 days. After training, rats consumed an antibiotic cocktail (ampicillin and streptomycin) in their drinking water (ABX: n=16), or filtered water for Controls (CTRL: n=16), for 21 days. Next, rats were placed in the same chambers where avoidance training occurred. Avoidance was tested by presenting 14 tones (30 sec, 4khz, 78 db, 3 min I.T.I.) alone in the

absence of the shock. Rats were euthanized 30 min after the last trial and brains were extracted. c-fos immunohistochemistry was used to label cellular actvity in brain regions involved in avoidance behavior, namely the ventral striatum.
RESULTS: Rats exposed to antibiotics spent more time on the safe platform throughout the test day (one-way ANOVA, p=0.0412), even though there was no risk of mild footshock. Moreover, we observed a tendency for increased cellular activity in the ventral striatum ($t_6 = 2.41$, p=0.0527). Together, these results suggest that persistent avoidance induced by antibiotic exposure could be driven by dysregulation of cellular activity the ventral striatum.
CONCLUSION: Our observations expand experimental models suggesting that antibiotic exposure disrupts brain function either directly or indirectly via alterations of the gut-brain-axis, thus driving negative valence behaviors.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.20/HH7

Topic: H.01. Fear and Aversive Learning and Memory

Title: Stimulus-specific autonomic responses to dental visual stimuli in adults with dental fear: A comparison with blood-injection-injury stimuli

Authors: *Y. KOIZUMI[1], S. TANAKA[2], H. KARIBE[2], A. OKAMOTO[2], T. SAITO[2];
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Abstract: Severe dental fear is associated with treatment avoidance and poor oral health. Dental visual stimuli include surgery, drilling, extraction, treatment environments, and oral trauma; however, it remains unclear whether autonomic responses differ by stimulus content. Dental fear has been linked to blood-injection-injury (BII) fear, but whether they share autonomic response patterns remains unknown. This study investigated stimulus-specific autonomic responses to dental visual stimuli in individuals with dental fear and examined responses to BII stimuli. We hypothesized that the dental fear group would exhibit autonomic response patterns distinct from those of controls in response to both dental and BII-related stimuli, with differences varying according to dental stimulus category. Forty-one healthy adults (21 men, 20 women; mean age 37.6 years) were classified into a dental fear group (Dental Fear Survey [DFS] ≥52, n=16) and a control group (DFS <52, n=25). Dental stimuli included surgery-, drilling-, extraction-, dental blood-, and neutral dental images. BII and neutral images were obtained from the International Affective Picture System. The images were presented in blocks of four. Electrodermal activity (EDA) and photoplethysmography (PPG) were recorded at 100 Hz using PowerLab 8/35. EDA

signals were decomposed using cvxEDA to estimate skin conductance responses (SCR) and sudomotor nerve activity (SNA). Baseline-corrected 0-6 s area under the curve was calculated for SNA. Inter-beat interval (IBI) and root mean square of successive differences (RMSSD) were derived from PPG. Group differences in SNA and RMSSD were analyzed using generalized estimating equations, whereas SCR and IBI were analyzed in 1-s epochs during the 6 s following stimulus onset using robust linear regression. Compared with the controls, individuals with dental fear showed greater SNA responses to extraction-related stimuli and higher RMSSD during surgery-related stimuli. During dental blood stimuli, the dental fear group exhibited enhanced SCR and increased IBI at 2-4 s after stimulus onset. No group differences were observed for BII stimuli. These findings indicate that autonomic responses associated with dental fear are stimulus-specific rather than uniform across dental contexts. Enhanced responses to extraction-related and dental blood stimuli suggest that threat-related dental cues preferentially engage autonomic mechanisms in individuals with dental fear. The absence of group differences for BII stimuli suggests that dental fear involves distinct autonomic processing of dental threat cues rather than a generalized BII-related autonomic response.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.21/HH8

Topic: H.01. Fear and Aversive Learning and Memory

Support: National Natural Science Foundation 32300844 of China
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Title: Serotonin shapes the temporal window for associative fear learning

Authors: *Y. ZHAO[1], X. LI[1], S. XIE[1], J. CAO[2], F. DENG[3], J. FENG[1], Y. LI[1];
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Abstract: Fear learning is a critical adaptive mechanism that enables the association of an environmental cue (the conditioned stimulus, CS) with a potential threat (the unconditioned stimulus, US), even when these events are temporally discontiguous. When associations are instead formed between unrelated cues and threats, the maladaptive learning process can give rise to neurological disorders. Therefore, maintaining accurate temporal boundaries for forming such associations is crucial for distinguishing real threats from irrelevant stimuli. Despite its importance, the mechanisms defining this precise time window remain poorly understood. Here, we report that serotonin plays a crucial role in modulating the associable interval in fear learning.

Specifically, we show that serotonergic projections from the dorsal raphe nuclei (DRN) to the CA1 region of the ventral hippocampus (vCA1) dynamically regulate the association of discontiguous CS and US. We demonstrate that sustained serotonin release in the vCA1 maintains the ensemble activity of 5-HT_2C receptor-expressing pyramidal neurons, therefore facilitating the association between temporally separated events. In contrast, when the trace interval exceeds the associable window, transient serotonin release fails to drive vCA1 neuronal ensemble activity, thus preventing maladaptive learning. Importantly, we further show that stress-induced disruption of the associable time window can be rescued by administration of the 5-HT_2C antagonist agomelatine, an atypical antidepressant clinically used to treat anxiety disorders. These findings highlight a key role for serotonin in regulating the temporal precision of fear learning and reveal the DRN-vCA1 serotonergic pathway as a potential therapeutic target for related disorders.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR323.22/HH9

Topic: H.01. Fear and Aversive Learning and Memory

Title: A central role for endocannabinoid signaling in operant shock avoidance behaviors

Authors: *S. PLASCENCIA, S. PARDO, P. A. CASTELLANOS, N. DELEON, A. GONZALEZ, J. M. WENZEL;
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Abstract: Several neuropsychiatric disorders are characterized by avoidance behaviors. For instance, people with major depressive disorder may avoid engaging in social interactions or partaking in tasks and experiences to avoid unpleasant emotions. Despite this, the neurobiological underpinnings of avoidance behaviors remain unclear. To address this, our lab and others have employed a simple avoidance task wherein rats press a lever to avoid footshock. Previous research using this task demonstrates that striatal dopamine signaling is integral for learning to avoid, but once the behavior is well-learned this system is no longer required to maintain avoidance. Additionally, research shows that midbrain endocannabinoid signaling is required for the dopaminergic signal that mediates avoidance learning but not maintenance, thus systemic or intra-ventral tegmental area pharmacological blockade of cannabinoid type-1 (CB1) receptors attenuates avoidance learning, but does not disrupt learned avoidance. However, simple lever-press avoidance tasks fail to capture the complexity of avoidance behaviors in humans, for instance, when a person with depression avoids others they may lose important social relationships. To better assess this complex choice, a platform-mediated avoidance task requires rats to choose between avoiding a negative stimulus or earning another reinforcer. In this task

rats press a lever for food on a variable interval schedule; after the presentation of a warning signal, the rat must disengage with lever pressing for food in order to climb onto a platform to avoid footshock. Therefore, this task requires that an animal choose between avoidance and earning other reinforcers. In this experiment we sought to determine the role of CB1 receptors in platform-mediated avoidance. Rats were trained on the platform-mediated avoidance task and then tested on two test days, one on which they received a systemic injection of vehicle and one on which they received a systemic injection of a CB1 antagonist. We found that CB1 antagonism significantly reduced latency to the platform, thereby biasing an animal towards avoidance behavior over operant responding for a food reinforcer. These data suggest that endocannabinoid signaling is important in choosing between avoidance and behaviors required to earn other natural rewards and may highlight a system to target for treatment of disorders of avoidance.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

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Program #/Poster #: PSTR323.23/HH10

Topic: H.01. Fear and Aversive Learning and Memory

Support: 5R00AG078501

Title: ACVR1C Signaling in the Basolateral Amygdala Regulates Amygdala-Dependent Extinction Fear Memory

Authors: *J. MOON, J. M. JUDD, A. KEISER;
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Abstract: Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder characterized by overly robust memories of a traumatic event that can be triggered by trauma-related cues. PTSD is associated with dysregulated amygdala activity, and altered Basolateral Amygdala (BLA) function is believed to contribute to the persistence of trauma-associated memories and extinction deficiency. We recently identified Activin A Receptor Type 1C (ACVR1C), a TGF-β type I receptor, as a bidirectional regulator of hippocampal-dependent memory. Disruption of *Acvr1c* in dorsal hippocampus by overexpression of an AAV1 kinase-dead mutant construct impaired performance in object location memory (OLM) and contextual fear conditioning (CFC) whereas overexpression of wildtype *Acvr1c* enhanced performance in OLM. Here we test the role of *Acvr1c* in BLA-dependent extinction of tone fear. Male and female C57BL/6J mice (8 weeks of age) received bilateral stereotactic injections of either a kinase-dead *Acvr1c* (KD) AAV1 construct or an empty-vector (EV) control into the BLA (AP: -1.4 mm, ML: ±3.1 mm, DV: -4.9 mm). Following three weeks of viral expression, mice underwent a behavioral battery of fear conditioning and extinction, elevated plus maze, open field, and beam balance. KD mice

maintained higher freezing to tone late in extinction when compared with their EV counterparts, suggesting impaired extinction memory. In elevated plus maze, the KD-mice spent less time in the open arm than EV mice, indicating a higher level of anxiety-like behavior. Collectively, these data suggest a critical role for ACVR1C in BLA for extinction and anxiety-like behavior. Ongoing studies will provide further insight into mechanisms by which ACVR1C regulates extinction of tone fear in female and male mice. These findings identify ACVR1C signaling in the BLA as a potential molecular regulator of fear extinction, suggesting that dysregulation of this pathway may contribute to the extinction deficits that characterize PTSD.

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Poster

PSTR323: Neurobiology of Fear and Avoidance Learning and Memory II

Location: WCC Halls A-C

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Program #/Poster #: PSTR323.24/HH11

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH National Institute of Drug Abuse (NIDA)

Title: Sodium Butyrate Effects on Sleep-Dependent Memory Consolidation in Sign-Trackers and Goal-Trackers

Authors: *A. M. MOUGHNI[1], M. ELKOURI[2], G. SHAHU[3], J. D. MORROW[4];
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Abstract: Individual differences in cue-directed learning may influence vulnerability to persistent fear memories, particularly when post-learning sleep and epigenetic regulation interact during memory consolidation. We tested whether sodium butyrate (NaB), a histone deacetylase inhibitor, enhances contextual fear-memory consolidation in a phenotype-, sleep-, and sex-dependent manner. Male and female rats were classified as sign-trackers, goal-trackers, or intermediate responders using a Pavlovian conditioned approach. Rats underwent contextual fear conditioning and were immediately treated with saline or NaB before either sleeping or undergoing sleep deprivation. Fear memory was assessed through freezing, scanning, and composite fear measures in a novel context and the conditioning context.
In males, NaB enhanced contextual fear expression specifically in sleeping goal-trackers, which showed greater freezing than saline-treated goal-trackers and other phenotypes (phenotype × sleep × drug interaction: $F(2,121.33) = 3.40$, $p = .036$; sleeping GT NaB vs. sleeping GT saline: MD = 24.33 ± 7.45, $p = .001$). In contrast, females did not show this Sleep + NaB enhancement but instead, sleep deprivation increased freezing in goal-trackers and sign-trackers (sleep × phenotype interaction: $F(2,143.54) = 8.05$, $p < .001$). Overall, these findings suggest that NaB modulation of fear-memory expression depends on post-learning sleep, behavioral phenotype, and sex, with the strongest enhancement observed in sleeping NaB-treated goal-tracker males.

Disclosures: A.M. Moughni: None. **M. Elkouri:** None. **G. Shahu:** None. **J.D. Morrow:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.01/HH12

Topic: H.06. Anxiety Disorders

Support: Wellcome Trust

Title: A MiND Resource: Animal Models in Neuropsychiatric Disorders Resource

Authors: *R. A. HILL[1], C. MCDONNELL[1], L. MILTON[1], U. THIVISOL[1], H. CRUICKSHANK[3], A. HEDBERG[5], C. J. FOLDI[2], J. KESBY[4], S. TYE[6], S. SUNDRAM[1]; [2]Physiol., [1]Monash Univ., Clayton, Australia; [3]The Univ. of Queensland Queensland Brain Inst., St Lucia, Australia; [4]The Univ. of Queensland Queensland Brain Inst., Moorooka, Australia; [5]Deakin Univ., Mount Duneed, Australia; [6]Queensland Brain Inst., St Lucia, Australia

Abstract: Animal models remain a contentious but important tool in mental health research. While translation has been hindered by the challenging task of modelling very complex human behaviours, animal models hold promise in providing new knowledge on causal biological pathways. Therefore, the critical question may not be whether or not animal models should be used, but which animal models are the most appropriate in mental health research? This calls for a revision of both animal models and behavioural assays in the mental health space to guide and refine their use and ultimately improve preclinical to clinical translation. Recognising these challenges and opportunities, the Consortium for Preclinical Psychiatric Research (CPPR) have launched a project with Wellcome Trust with the aim of producing a reliable, free-to-use, online resource of animal models and assays for the domains of depression, anxiety, and psychosis. Evaluation frameworks were developed with input from domain experts and lived experience working groups from across the globe. Advanced AI screening tools were used to search and extract literature pertaining to face, construct, predictive, and ecological validity of currently used behavioural assays and models. Here, we present results from the evaluation of common assays. Evaluations of assays under the domain of anxiety showed high face, and ecological validity scores for the open field test, but moderate scores for construct and predictive validity. In contrast, the light dark box scored high for ecological and predictive validity but moderately for face, construct and cross-species validity. Within the domain of psychosis assays such as pre-pulse inhibition, locomotor activity and latent inhibition scored moderately-high for construct and predictive validity, but low-moderately for face validity, highlighting face validity as a weakness for psychosis assay translatability. In the depression domain, the tail suspension test scored low across face, ecological and construct validity but scored moderate -high in predictive validity, suggesting this assay is a good tool for assaying treatment response, but may not be useful in understanding the underlying biological mechanisms that drive depressive behaviours.

The sucrose preference test, however, scored moderate-high for face validity, moderate for construct validity and high for predictive validity. This evaluative resource (website currently under development) provides a platform for researchers to determine the assay most appropriate for their research question contingent on the best validity domain/s.

Disclosures: R.A. Hill: None. **C. McDonnell:** None. **L. Milton:** None. **U. Thivisol:** None. **H. Cruickshank:** None. **A. Hedberg:** None. **C.J. Foldi:** None. **J. Kesby:** None. **S. Tye:** None. **S. Sundram:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.02/HH13

Topic: I.09. Spatial Navigation

Title: A Cognitive Model of OCD: Negative Reinforcement of Extensive Place Taining and Aversive Affect Result in Sex/Individual Differences in Compulsive Checking Behavior in Rats

Authors: K. Q. ANDERSON, A. KAMAL, *B. D. DEVAN;
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Abstract: Animal models of OCD have focused on compulsions, repetitive behaviors strengthened through reinforcement. Criticisms of these models have focused on the lack of a compelling cognitive component related to negative ruminations in human subjects, which may help evoke compulsive acts or remain independent as excessive repetitive/recursive obsessive thoughts, possibly related to the controversial construct of “pure-O.” In the present study, we adopted a widely accepted neurocognitive-spatial paradigm, the water maze place task, to overtrain a higher-order place habit across 120 trials. The results show that extensive place training in the water maze leads some individual rats to check the former goal location repeatedly. Female subjects tended to engage in checking behavior more than males and would also navigate close to the pool wall, a behavior associated with anxiety (i.e., thigmotaxis) that occurred in both females and males. In additional studies, individual differences were correlated with dry open-field behavior, including object exploration and thigmotaxis, under different conditions. While some results support a role for increased anxiety, other findings suggest that orientation to the pool's outer border may be related to complete removal, tactile stimulation, and/or attraction to the wall as a salient local cue. Further studies revealed that increasing aversive stimulation (negative affect) via increased water submersion (3 cm depth) during passive placement on the platform at the novel location following original place training, also produced individual differences in checking behavior and/or more subtle lurching micro-behaviors below the threshold of an overt compulsive-checking swim response. Together, the findings suggest an interaction among cognition, affect, and negatively reinforced habit

formation in determining sex and individual differences in OCD-like checking behavior in the water maze, a widely accepted cognitive-spatial paradigm in translational neuroscience.

Disclosures: K.Q. Anderson: None. **A. Kamal:** None. **B.D. Devan:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.03/HH14

Topic: H.06. Anxiety Disorders

Support: VIEP-BUAP 2026
SECIHTI fellowship No. 4024719

Title: Hedonic response and sucrose preference in high-yawning and low-yawning sublines of Sprague-Dawley rats

Authors: *F. ISLAS[1], C. CORTES[3], A. UGARTE[2], J. R. EGUIBAR, Sr.[4];
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Abstract: Consumption and preference for sugar-sweetened beverages in rodents are commonly assessed using the two-bottle paradigm, which is the basis of the sucrose preference test. This approach is essential for analyzing the relationship between the consumption of palatable beverages driven by their hedonic value and behaviors related to anxiety, addiction, and depression. At the Institute of Physiology, we selectively inbreed two sublines from the Sprague-Dawley strain of rats that differ in their spontaneous yawning frequency. The high-yawning (HY) rats had a mean frequency of 20 yawns per hour (y/h), while low-yawning (LY) rats yawn only 2 y/h. These sublines differ in their responses to stress and anxiety when evaluated in standardized tests, with LY rats being more anxious than HY rats. The aim of the study was to compare the preference for a 10% sucrose solution between HY and LY rats. Thirty-two male rats aged 100 ± 1 postnatal days (PND) were used being HY (n=16) and LY (n=16). Each subline had an experimental group exposed to sucrose (S) solution (LY S and HY S) with access to both the sucrose solution and water (Sucrose/Water, n=8), and a control group (LY C and HY C) with access only to purified water (Water/Water, n=8). Rats were pair-housed under standard conditions with free access to chow. Over 30 days, two bottles were placed in each cage, one containing 100 mL of water and the other containing 100 mL of 10% sucrose solution. The volume consumed from each bottle was measured daily, and the preference index (PI) was calculated as: Sucrose consumption/Total fluid consumption×100. Our results showed that LY rats had a higher PI than the HY subline ($F_{(1,12)}$=6.721; P<0.05) and that the difference against their respective control group (LY C) was also higher ($F_{(1,12)}$=76.237; P<0.001). These two

factors interact ($F_{(1,12)}$=11.243; P<0.01) because LY S group had a higher sucrose preference index than the HY S group (65.79% vs. 58.10%, respectively; P<0.001) supporting that the anxiety phenotype of the LY rats may confer a heightened sensitivity to palatable rewards and a greater addiction to sucrose solution. So, these yawning sublines are a valuable model for exploring the neurobiological links between anxiety traits and reward-seeking behaviors.

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

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.04/HH15

Topic: H.06. Anxiety Disorders

Support: First-Year Research Immersion Program, Binghamton University

Title: Novel Rat Model of a Reduction of Social Enrichment Disrupts Stress Response in Males

Authors: *A. LINENBERG[1], E. MCCLENATHAN[1], D. S. KREISS[2];
[1]Dept. of Psychology, Binghamton Univ., Binghamton, NY; [2]First-Year Res. Immersion Program, Neurosci., Binghamton University, First-Year Res. Immersion Program, Binghamton, NY

Abstract: The rise of anxiety disorders in adolescents following the COVID-19 pandemic demands further comprehensive study of the unique social situation induced by lockdown protocols. The present study utilized male and female rats to develop a model of a sudden reduction of social enrichment. High enrichment included 5 minutes of handling followed by 20 minutes of social play 4x/week, in addition to larger cages and access to toys. Social play occurred between 10 rats of the same experimental group in a playpen with free access to toys. Experimental rats were exposed to high social enrichment beginning at post-natal day (PND) 39 before a sudden reduction to standard laboratory social enrichment at PND 84. Control and Standard rats experienced continuous high and standard social enrichment, respectively, throughout the experiment. Rats were tested on the Elevated T-Maze on PND 74-77 (Trial 1) and again on PND 102-105 (Trial 2). Following placement on the open arm, latency to enter a closed arm (t < 90 sec) was measured across 5 consecutive runs in each trial. Latency to enter a closed arm was analyzed as a measure of response to stress, with a decrease in latency indicating increased stress. When compared to Trial 1, average latency in Trial 2 decreased in Experimental males but increased in Control and Standard males. In Trial 2, average latency of Experimental males was 61% shorter than Control males and 55% shorter than Standard males. Experimental males also failed to follow the age-dependent pattern exemplified by Control and Standard groups. Results suggest that a sudden reduction of enrichment compromises maturation of stress response in male rats, inducing an increased avoidant response and inability to habituate to an

anxiogenic stimulus. Results from females did not establish a clear age-dependent pattern, suggesting that an optimal model of social reduction in female rats requires further investigation. Findings implicate the role of a sudden reduction of enrichment in the expression of anxiety-like behaviors in male rats, thus partially validating a novel animal model of pandemic lockdowns.

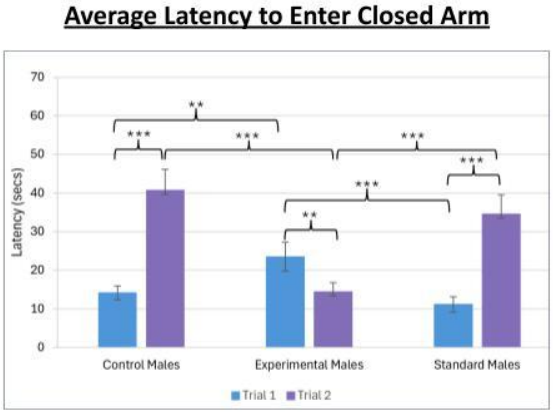


Figure 1. Average latency to enter a closed arm of the Elevated T-Maze in Trial 1 (blue) and Trial 2 (purple) of Control Males, Experimental Males, and Standard Males. Data presented as mean of trial ± SEM. **p < 0.01, ***p < 0.001



Figure 2. Latency to enter a closed arm on each of 5 runs in Trial 1 (blue) and Trial 2 (purple) of Experimental Males (top panel), Control Males (bottom left panel), and Standard Males (bottom right panel). Data presented as mean of run ± SEM. Comparisons to first run of each respective trial indicated by #0.05 < p < 0.08, *p < 0.05.

Disclosures: A. Linenberg: None. **E. McClenathan:** None. **D.S. Kreiss:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.05/HH16

Topic: H.06. Anxiety Disorders

Support: FAPESP (Grant: 2017/25409-0 and 2025/21133-6)
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CNPq research fellowship (306556/2015-4 and 305210/2026-2)

Title: Acute and chronic social defeat stress provoke differential corticosterone responses in male and female Swiss-Webster mice.

Authors: *R. L. NUNES-DE-SOUZA[1], K. C. SILVA[2], J. AVALO-ZULUAGA[1], D. B. SOUZA[3], L. CANTO DE SOUZA[4];

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Abstract: Previous studies have demonstrated that in male Swiss-Webster mice, chronic social defeat stress (SDS) induces pronounced anxiogenic and cognitive deficits and hyperactive glutamatergic signaling in the bed nucleus of the stria terminalis (BNST) and amygdala, alongside a dorsal-ventral hippocampal imbalance. However, it remains unclear how the neuroendocrine response to this direct stress differs by sex and temporal exposure in this strain. This exploratory study investigated the impact of acute and chronic direct social defeat stress (SDS) on hypothalamic-pituitary-adrenal (HPA) axis activation in male and female mice to identify sex-specific stress vulnerabilities.Male and female Swiss-Webster mice (60–65 days postnatal) were randomly assigned to control (Naïve), non-aggressive interaction (NAI), or direct social defeat stress (SDS). Subjects were exposed to either an acute (1 session) or chronic (10 sessions) protocol (n = 6 per group). The study adhered to ARRIVE 2.0 guidelines, maintained controlled environmental conditions, and quantified circulating corticosterone levels utilizing a validated competitive enzyme-linked immunosorbent assay (ELISA).In the acute SDS protocol, male mice exhibited a significant elevation in corticosterone levels compared to both NAI and Naïve groups ($F_{(2, 15)} = 14.51$, $p < 0.001$, $\eta^2p = 0,65$). Females also demonstrated robust HPA axis activation following acute SDS compared to Naïve controls, though a similar significant elevation was observed in their respective NAI control group ($F_{(2, 15)} = 29.86$, $p < 0.0001$, $\eta^2p = 0,79$). Conversely, following chronic SDS exposure, a pronounced sexual dimorphism emerged. Males maintained higher corticosterone levels than both control groups ($F_{(2, 15)} = 46.95$, $p < 0.001$, $\eta^2p = 0,65$). In contrast, females did not exhibit a significant effect of condition after chronic SDS ($F_{(2, 15)} = 3.10$, $p = 0.075$, $\eta^2p = 0,29$), indicating an absence of HPA axis hyperactivation.While acute direct social stress activates the neuroendocrine system in both sexes, chronic exposure reveals a distinct sexual dimorphism. Male mice display sustained HPA axis hyperreactivity, whereas females appear to habituate to the repeated physical stressor, returning to baseline corticosterone levels. These findings highlight the critical importance of evaluating sex and stressor chronicity to fully understand the neurobiology of stress-related disorders.

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Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.06/HH17

Topic: H.06. Anxiety Disorders

Title: A GABAergic Preoptic-Raphe Circuit Mediates the Paradoxical Coupling of Anxiety and Social Preference Induced by Comparative Social Deficit in Male MiceAuthors

Authors: Y. ZHANG[1], ***M. HU**[2], S. XIE[3], C. YU[4], H. LIAN[6], X. LI[5];
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Abstract: A GABAergic Preoptic-Raphe Circuit Mediates the Paradoxical Coupling of Anxiety and Social Preference Induced by Comparative Social Deficit in Male MiceAuthors Yan-Yi Zhang[1,2,3], **Meng-Ting Hu[1,2,3]**, Shi-Ze Xie[1,4], Chen-Xi Yu[1,3], Hong Lian[1,2,5]*& Xiao-Ming Li[1,3]*1Department of Neurology and Department of Psychiatry, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China. 2Nanhu Brain-computer Interface Institute, Hangzhou, China. 3NHC and CAMS Key Laboratory of Medical Neurobiology, MOE Frontier Center of Brain Science and Brain-machine Integration, School of Brain Science and Brain Medicine, Zhejiang University, Hangzhou, China. 4Liangzhu Laboratory, Zhejiang University Medical Center, Hangzhou, China.5Research Center of System Medicine, School of Basic Medical Sciences, Zhejiang University, Hangzhou, China.**DisclosuresYan-Yi Zhang:** None. **Meng-Ting Hu:** None. **Shi-Ze Xie:** None. **Chen-Xi Yu:** None. **Hong Lian:**None. **Xiao-Ming Li:** None. **Abstract**Anxiety disorders are the most prevalent mental disorders globally, with social disconnection recognized as a major risk factor. Yet the neural substrates through which social disconnection drives anxiety remain poorly defined. Here we establish a comparative social deficit (CSD) model in adult male mice that mimics relative social exclusion by maintaining sensory contact between a socially excluded subject and freely interacting conspecifics. Unlike complete isolation, CSD evokes a distinctive behavioral phenotype characterized by increased anxiety-like behavior alongside heightened social preference, paralleling the paradoxical state of heightened anxiety coupled with increased social motivation of human loneliness. Furthermore, CSD selectively increased the excitability of medial preoptic GABAergic (mPOAGad2) neurons, and these neurons bidirectionally regulate CSD-induced behavioral changes. Transcriptomic and electrophysiological analyses identified downregulation of the Kv4.3 potassium channel (Kcnd3) as a molecular driver of mPOAGad2 hyperexcitability. The mPOAGad2 neurons exert monosynaptic inhibition onto dorsal raphe serotonergic (DRN5-HT) neurons, reducing their excitability, and restoring DRN5-HT neuron activity rescued the behavioral effects of CSD. Together, our findings define a molecular and circuit mechanism by which social disconnection remodels mPOA-DRN interactions to drive the paradoxical coupling of anxiety and social preference, and provide a translational framework for probing loneliness-related vulnerability to psychiatric disorders.

Disclosures: Y. zhang: None. **M. hu:** None. **S. Xie:** None. **C. yu:** None. **H. Lian:** None. **X. Li:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.07/HH18

Topic: H.06. Anxiety Disorders

Title: Implication of insula circuits in high caloric diet-induced anxiety

Authors: *L. PAGES[1], E.-G. DUCOURNEAU[5], L. ROUZOUL[6], L. WILMES[1], J. BUTLER[7], W. HU[2], D. RICCI[3], Y. COUDERC[4], T. BITTAR[3], J. BORDES[1], C. PENET[8], G. FERREIRA[9], A. BEYELER[10];
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Abstract: Anxiety is an essential emotion allowing animals to avoid harmful situations. However, anxiety can become pathological, when persistent independently of the environment. In fact, anxiety disorders represent the most prevalent psychiatric condition. Although the etiology of anxiety disorders remains largely unknown, risk factors have been identified. For example, 20% of obese subjects develop an anxiety disorder. Interestingly, the insular cortex (insula) activity is altered in patients affected by anxiety disorders, obesity, and in animal models of both disorders. Thus, we hypothesize that the insula contributes to obesogenic diet-induced anxiety.

To assess the impact of overweight on anxiety, we subjected 8-weeks-old C57BL/6J mice in both sexes to a chronic high caloric diet (HCD). We evaluated anxiety of standard-diet (SD)-fed mice or HCD-fed mice by performing the elevated plus maze (EPM) and novelty suppressed feeding test. Interestingly, HCD mice spent less time in open arms of the EPM, confirming that the obesogenic-diet-induced anxiety-related behaviors.

To define the contribution of insula circuits in HCD-induced anxiety, we performed calcium imaging of excitatory neurons of the anterior or posterior insula (aIC and pIC) as well as neurons of the anterior insula projecting to the nucleus accumbens or to the basolateral amygdala (insula-NAc and insula-BLA), in both groups. The activity of insula neurons in SD-fed mice was higher when mice were in open arms, selectively in the aIC. Interestingly, this response was amplified in HCD-fed mice, and correlated with anxiety.

Consistently, using ex vivo electrophysiological recordings we found that aIC, but not pIC pyramidal neurons were more excitable in HCD mice. To identify the mechanisms underlying the hyperexcitability of the aIC after HCD, we also quantified neuro-inflammation in the insula. Finally, with chemogenetic manipulations we assessed the causal role of neural population which exhibit increased activity after HCD. Overall, our work supports the hypothesis of a crucial contribution of excitatory neurons of the anterior insula in HCD-induced anxiety in mice. Overall, our work supports the hypothesis of a crucial contribution of the insula cortex in HCD-induced anxiety in mice.

Disclosures: L. Pages: None. **E. Ducourneau:** None. **L. Rouzoul:** None. **L. Wilmes:** None. **J. Butler:** None. **W. Hu:** None. **D. Ricci:** None. **Y. Couderc:** None. **T. Bittar:** None. **J. Bordes:** None. **C. Penet:** None. **G. Ferreira:** None. **A. Beyeler:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.08/HH19

Topic: H.06. Anxiety Disorders

Support: French Ministry of Higher Education and Research (MESR)

Title: Function of the insular cortex in the impact of a single psychedelics injection on anxiety

Authors: *D. RICCI, O. ISAAC NEWTON, B. LAUNAY, B. EGINARD, C. PENET, Y. COUDERC, J. BORDES, L. PAGES, J. BUTLER, R. SIADOUS, A. BEYELER;
Inserm U1215, Bordeaux Cedex, France

Abstract: Anxiety is an evolutionarily conserved survival response that promotes adaptive reactions to potential danger, becoming pathological when it persists in the absence of real or anticipated threat. Anxiety disorders affect ~18% of adults worldwide, yet current therapeutic options remain insufficient. Selective serotonin reuptake inhibitors are among the most commonly prescribed treatments, but their delayed onset of action, side effects, and substantial rate of treatment resistance highlight the need for alternative strategies. Serotonergic psychedelics, including 5-MeO-DMT (5-MeO), have recently re-emerged as promising anxiolytic compounds. Preclinical and clinical evidence suggests that a single administration can induce benefits lasting from days to weeks. Importantly, these sustained effects can be partly dissociated from acute psychedelic-like responses, indicating that long-term anxiolysis is likely supported by circuit-level adaptations and plasticity mechanisms that extend beyond the acute subjective state. These effects are thought to involve serotonergic signalling through 5-HT1A and 5-HT2A receptors. The anterior insular cortex is a key hub for anxiety-related behaviors, integrating interoceptive and emotional signals, and a large fraction of its neurons express 5-HT1A/2A receptors. It therefore provides a strategic area to dissect both the acute and long-term circuit mechanisms supporting psychedelic-induced anxiolysis. **We hypothesize that 5-MeO produces sustained anxiolysis by attenuating maladaptive insular hyperactivity through insular 5-HT1A+ neurons**. To test this, we established three complementary approaches: [1] behavioral phenotyping after single 5-MeO administration at acute (1 h) and delayed (7 d) time points; [2] fiber-photometry recordings of insular 5-HT1A+ neurons activity during psychedelic-like and anxiety-related behaviors; and [3] in vivo electrophysiology to quantify insular oscillatory dynamics and single-unit spiking across brain states during psychedelic-like and anxiety-related behaviors. Together, our results provide a strong mechanistic foundation for

understanding how psychedelics reshape insular circuit function over days to support sustained anxiolysis.

Disclosures: D. Ricci: None. **O. Isaac Newton:** None. **B. Launay:** None. **B. Eginard:** None. **C. Penet:** None. **Y. Couderc:** None. **J. Bordes:** None. **L. Pages:** None. **J. Butler:** None. **R. Siadous:** None. **A. Beyeler:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.09/HH20

Topic: H.06. Anxiety Disorders

Title: CCK-4-induced cognitive deficit in mice as a translational model for panic anxiety-associated cognitive impairment

Authors: *E. ANDRIAMBELOSON, E. POIRAUD, B. HUYARD, S. WAGNER; NEUROFIT, ILLKIRCH, France

Abstract: Introduction: Cognitive dysfunction, including working memory lapses and poor attentional control, is an underrecognized but disabling aspect of panic disorder. Addressing these deficits is critical for improving patient outcomes. The cholecystokinin tetrapeptide (CCK-4) not only provokes panic attacks in humans and rodents but has also been shown to impair short-term memory in healthy volunteers, highlighting its direct impact on cognition. In rodents, CCK-4 activates limbic and prefrontal circuits related to both fear and cognition in rodents, making it an excellent translational tool to model this pathology. **Objectives:** The objective of this study was to establish CCK-4-induced cognitive impairment in mice as a valid and clinically relevant preclinical model for identifying therapies that can restore cognitive function in the context of panic anxiety. **Methods:** Mice received CCK-4 injection and were evaluated in the T-maze spontaneous alternation test, a sensitive assay of cognitive performance that primarily reflects working memory, while also engaging attentional control, impulse regulation, and executive function. Pharmacological profiling was performed with diazepam and clonidine (both clinically effective panicolytics) and donepezil (a cognitive enhancer). As controls, diazepam was also tested against scopolamine-induced (amnesia model) and MK-801-induced (psychosis model) deficits. **Results:** CCK-4 administration produced a robust, dose-dependent reduction in spontaneous alternation, consistent with impaired cognitive performance. This deficit was reversed by diazepam and clonidine, supporting the involvement of stress-related mechanisms, and by donepezil, indicating that cholinergic augmentation may counteract anxiety-related cognitive dysfunction. In contrast, diazepam failed to reverse scopolamine- or MK-801-induced deficits (reflecting amnesia- and psychosis-associated cognitive impairments, respectively), underscoring that the CCK-4 paradigm models a distinct, anxiety-driven cognitive pathology.

Conclusions: These findings establish CCK-4-induced impairment as a translational model for identifying therapies that can both reduce panic anxiety and restore cognitive control.

Disclosures: E. Andriambeloson: None. **E. Poiraud:** None. **B. Huyard:** None. **S. Wagner:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.10/HH21

Topic: H.06. Anxiety Disorders

Support: Grant CBF-2025-I-4046

Title: Evaluation of the anxiolytic effect of hydrogensulfide in Wistar rats

Authors: *V. CARMONA TORRES, C. LOPEZ-RUBALCAVA, D. CENTURIÓN; Pharmacobiology, Ctr. for Res. and Advanced Studies of the Natl. Polytechnic Inst., Mexico City, Mexico

Abstract: Hydrogen sulfide (H2S) is an endogenous gasotransmitter that modulates neuronal activity in the brain. As a small, freely diffusible molecule, it influences synaptic transmission and neuronal excitability and has been increasingly linked to the regulation of emotional behavior. However, its potential role in anxiety remains poorly characterised. This study evaluated the anxiolytic-like effect of the H2S donor sodium hydrosulfide (NaHS) in male Wistar rats. A total of 40 male Wistar rats were assigned to two experiments. In Experiment 1 (Conditioned Defensive Burying [CDB] and self-grooming analysis), three groups (n=8 each) were tested: NaHS (treated), PBS (vehicle), and saline (SS) controls. In Experiment 2 (elevated plus maze [EPM] and open field test of locomotor activity), two groups (n=8 each) were tested: NaHS (treated) and PBS (vehicle). NaHS (5.6 mg/kg) was dissolved in phosphate-buffered saline (PBS) and administered intraperitoneally. Data are mean +/- standard error of the mean (SEM; error bars denote SEM). Three-group comparisons used one-way ANOVA with the Tukey test when parametric assumptions were met, or Kruskal-Wallis with Dunn's test otherwise; two-group comparisons used Student's t-test ($p<0.05$). NaHS markedly reduced self-grooming duration (14.6 +/- 5.5 s) compared with PBS (100.1 +/- 20.0 s) and SS (66.7 +/- 8.6 s; $p<0.001$) and grooming frequency (2.6 +/- 0.8 vs 12.6 +/- 2.9 and 7.6 +/- 0.6; $p=0.003$), while grooming latency increased. In the EPM, NaHS reduced the time spent in the closed arms (522 +/- 5 vs 563 +/- 9 s; $p=0.002$) and increased closed-arm entries (7.0 +/- 1.1 vs 3.9 +/- 0.8; $p=0.035$); open-arm entries, open-arm time, and rearing increased without reaching significance. In the CDB, burying time was shorter after NaHS (144.6 +/- 35.9 s) than after PBS (231.0 +/- 33.1 s) or SS (160.4 +/- 17.7 s; $p=0.12$), with burying latency unchanged. General locomotion in the open field was preserved (52.6 +/- 4.1 vs 47.0 +/- 3.0 crossings), indicating no motor impairment. These

findings indicate that NaHS produces an anxiolytic-like profile in male rats without affecting general locomotor activity, supporting a role for H2S signaling in the regulation of anxiety-like behavior.

Disclosures: V. Carmona Torres: None. **C. Lopez-Rubalcava:** None. **D. Centurión:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.11/HH22

Topic: H.06. Anxiety Disorders

Support: CNPq (Process No. 307714/2023-3)

Title: Cannabigerol as a potential therapeutic strategy for anxiety related to acute stress: evidence in male and female rats

Authors: M. H. HIRABAYASHI[1], F. J. STORGATTO[1], ***V. BITENCOURT**[2], J. M. CUNHA[1], J. M. ZANOVELI[1];
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Abstract: Given the growing interest in the therapeutic potential of cannabinoids, this study aimed to investigate the temporal effects of cannabigerol (CBG) on acute stress-induced anxiety and to evaluate potential sexual dimorphism. Two days after habituation, 60-day-old male and female Wistar rats were subjected to a 120-minute acute restraint stress protocol, while a control group remained unstressed. Twenty-four hours later (Day 1), a 7-day treatment commenced with CBG (0, 3, 10, or 30 mg/kg, i.p.) or fluoxetine (FLX; 10 mg/kg, positive control). On Day 1, 30 minutes post-treatment, animals underwent the Open Field Test (OFT) to assess the acute effects of CBG on exploratory and anxiety-like behaviors. On Day 8 (20 hours after the final administration), prolonged effects on anxiety were evaluated using the Elevated Plus Maze (EPM) test. Four days post-treatment, the Light-Dark Transition (LDT) test was performed to assess potential withdrawal effects. Unlike FLX, CBG induced an acute anxiolytic-like effect across all three doses in females and at the 10 and 30 mg/kg doses in males, without altering locomotor activity. Following continuous treatment, males exhibited variable responsiveness to the anxiolytic-like effect, whereas females remained consistently responsive across all tested doses. Upon treatment cessation, a rebound or sustained anxiolytic-like effect was observed, depending on dose and sex. Notably, unlike FLX, CBG did not reduce body weight gain, and its anxiolytic-like effects were not associated with either stimulant or sedative properties. Collectively, these findings indicate that CBG produces a rapid-onset and long-lasting anxiolytic-like effect under stress conditions, while also revealing marked sexual dimorphism in treatment responsiveness. Overall, despite sex-dependent differences in treatment

responsiveness, CBG may represent a promising therapeutic alternative for the management of acute stress-related anxiety disorders in both sexes. Financial support: CNPq (Process No. 307714/2023-3)

Disclosures: M.H. Hirabayashi: None. **F.J. Storgatto:** None. **V. bitencourt:** None. **J.M. Cunha:** None. **J.M. Zanoveli:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.12/HH23

Topic: H.06. Anxiety Disorders

Title: Ketamine rescues anxiety-like behavior and reshapes parvalbumin-specific oxidative stress profiles across two rat models of anxiety vulnerability

Authors: H. HAIDARI, L. GOLAN, F. ABDIRAHAMAN, A. LEMESHOVA, S. ELLIS, *J. A. HONEYCUTT;
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Abstract: Anxiety disorders, characterized by maladaptive behavioral patterns in response to ambiguous threat, have a lifetime prevalence of 34%, with about 30% of patients resistant to antidepressant (SSRI/SNRI) therapies. Sub-anesthetic ketamine shows efficacy in treating treatment resistant patients with depression and PTSD, with emerging evidence for its use as an anxiolytic. Ketamine is a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist, and shows high affinity for NMDA receptors on fast-spiking inhibitory cells containing parvalbumin (PV). PV cells in the prefrontal cortex (PFC) are important for maintaining excitatory-inhibitory balance, and their function is impacted in affective disorders. While there is limited understanding of the mechanisms through which ketamine exerts its therapeutic effects, it likely impacts functional properties of PV, particularly in the PFC where they coordinate local tone. Further, sex contributes to ketamine's effects, with reports of females requiring lower doses for beneficial outcomes. Notably, females have higher lifetime prevalence of affective disorders and are underrepresented in preclinical studies. In rodents, females use different behavioral strategies from males under certain conditions, such as active avoidance in fear conditioning and acoustic startle paradigms. Here, we found comparable sex-specific changes in behavior, as well as in PV cell counts and oxidative stress patterns in the PFC and basolateral amygdala (BLA) of rats. These effects were further differentiated based on whether a developmental (early life adversity; ELA) or genetic (Wistar-Kyoto; WKY) model was used. We sought to determine if the mechanism of PV dysfunction differs between models and behavioral responses, and in its ability to be rescued by ketamine treatment. Using the open field test with 22kHz alarm call playback , we characterized behavior of ELA rats as either darting (active avoidance) or freezing (passive avoidance). In the brain, ELA decreased PV counts in the PFC and altered levels of

oxidative stress across other affective brain regions both globally and with specificity to PV. In female WKYs, ketamine treatment reduced anxiety-like behaviors in the acoustic startle box and increased oxidative stress in BLA PV cells. Additionally, ketamine also served to normalize behavioral responses to distal threat (via 22 kHz ultrasonic vocalization playback) only in ELA females. Thus, the therapeutic effects of ketamine may be conferred via different mechanisms depending on 1) model system; 2) dose of ketamine (with 10 and 15mg/kg being most efficacious across outcomes); and sex in rats.

Disclosures: H. Haidari: None. **L. Golan:** None. **F. Abdirahaman:** None. **A. Lemeshova:** None. **S. Ellis:** None. **J.A. Honeycutt:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.13/HH24

Topic: H.06. Anxiety Disorders

Support: Beca SECIHTI 4060235

Title: Pubertal Paracetamol Exposure Does Not Alter Anxiety-, Depression-Like Behavior, or Basal Corticosterone Levels in Adult Male Rats

Authors: *J. SIERRA[1], A. D. GUZMÁN MONTEMAYOR[1], M. BARRADAS-MOCTEZUMA[3], D. HERRERA-COVARRUBIAS[1], R. TOLEDO-CARDENAS[1], G. A. CORIA-AVILA[2];
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Abstract: Background: Paracetamol (a.k.a. acetaminophen) is a widely used analgesic and antipyretic drug that inhibits cyclooxygenase (COX-2/3) pathways and blocks the synthesis of prostaglandin E2 (PGE2). Although prenatal exposure has been associated with emotional and hormonal alterations in adulthood, including lower anxiety indices, increased depression-like behaviors, and reduced corticosterone responses during social encounters, the specific impact of its administration during the pubertal window remains unknown. Objective: This study evaluated the effects of pubertal paracetamol administration on anxiety- and depression-like behaviors in adult male rats, as well as its impact on serum corticosterone levels. Methods: Male Wistar rats received subcutaneous injections of paracetamol (50 mg/kg) or saline solution (control) every 12 hours during puberty (postnatal days 36-40). In adulthood, half of the animals received sexual experience across five trials, whereas the other half remained sexually naïve. Anxiety-like behavior was assessed using the elevated plus maze (EPM), and depression-like behavior was evaluated with the forced swim test (FST). Basal serum corticosterone levels were quantified

several days later using an enzyme-linked immunosorbent assay (ELISA). Results: Behavioral analysis in the EPM revealed no significant differences in the time spent in the open arms, closed arms, or center of the maze between paracetamol- and saline-treated groups, regardless of prior sexual experience. Similarly, the FST showed no significant differences in immobility or climbing frequency. Consistent with these findings, serum corticosterone levels in adulthood were also unchanged. Conclusion: In contrast to prenatal treatment, our findings suggest that pubertal administration of paracetamol does not significantly alter anxiety- or depression-like behaviors, nor basal corticosterone regulation, in adulthood. These results suggest that disruption of COX-2/3 pathways specifically during the pubertal window does not induce long-term alterations in emotional reactivity or basal hypothalamic-pituitary-adrenal axis activity in this model.

Disclosures: J. Sierra: None. **A.D. Guzmán Montemayor:** None. **M. Barradas-Moctezuma:** None. **D. Herrera-Covarrubias:** None. **R. Toledo-Cardenas:** None. **G.A. Coria-Avila:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: H.06. Anxiety Disorders

Support: Secretaría de Educación, Ciencia, Tecnología e Innovación (SECTEI) de la Ciudad de México, grant number SECTEI/158/2024

Title: Selective gut microbiota remodeling and metabolic improvement in adults with obesity, depression, and anxiety symptoms after a Traditional Mexican Diet-based weight loss program

Authors: *L. SANCHEZ-CHAPUL[1], M. SAMUDIO-CRUZ[2], E. CABRERA-RUIZ[3], D. CERQUEDA-GARCÍA[4], A. LUNA[2], P. CARRILLO-MORA[2], K. ANDRADE[5], V. ANDRADE[6], E. RANGEL-LOPEZ[7];
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Abstract: The Traditional Mexican Diet (TMD) has emerged as a promising alternative for cardiovascular health and chronic disease prevention, but its combined effects with physical activity on the gut-brain-metabolic axis remain unclear. This study aimed to evaluate the effects of a 12-week weight loss program (WLP), based on a hypocaloric TMD and moderate-intensity exercise, on body composition, gut microbiota, and metabolic health in Mexican adults with

obesity and symptoms of depression and anxiety. We characterized the gut microbiota of 106 adults with obesity, classified by the presence or absence of depressive and anxiety symptoms into three groups: obesity control group without symptoms (OCG), improved symptoms (OIS), and persistent symptoms (OPS), by sequencing the V3-V4 region of the 16S rRNA gene (Illumina MiSeq). Longitudinal changes in body composition, serum biochemistry, intestinal permeability markers, and gut microbiota were analyzed using linear mixed-effects models. Differential taxa were identified using linear discriminant analysis effect size (LEfSe), and associations between bacterial genera, biochemical variables, and dietary components were assessed with MaAsLin2. The WLP significantly improved body composition, metabolic and inflammatory biomarkers, intestinal permeability, and depressive and anxiety symptoms, although all participants remained in WHO grade I obesity. We identified group-dependent modulation of bacterial genera rather than broad microbiota restructuring, with 22 taxonomic biomarkers defining each group: 16 in OPS, 5 in OIS, and 1 in OCG. The WLP, combining a hypocaloric TMD with exercise, promoted metabolic and body composition improvements in all participants, along with group-specific gut microbiota remodeling that may be associated with differential changes in depressive and anxiety symptoms in the context of persistent obesity.

Disclosures: L. Sanchez-Chapul: None. **M. Samudio-Cruz:** None. **E. Cabrera-Ruiz:** None. **D. Cerqueda-García:** None. **A. Luna:** None. **P. Carrillo-Mora:** None. **K. Andrade:** None. **V. Andrade:** None. **E. Rangel-Lopez:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.15/HH26

Topic: H.06. Anxiety Disorders

Support: R01 MH100117-01

Title: Dynamic Functional Connectivity in Salience, Default Mode, and Frontoparietal Networks as a Neural Pathway between Early-Life Adversity and Internalizing Symptoms

Authors: *P. QAMAR[1], P. KIRK[4], K. NULL[2], R. ZINBARG[5], R. NUSSLOCK[5], R. LEBEAU[1], T. C. HO[3], M. CRASKE[1];
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Abstract: Early-life adversity (ELA) increases internalizing risk, yet the neural mechanisms remain unclear. Threat and deprivation are dimensions of ELA, with partially distinct consequences (Sheridan & McLaughlin, 2014). Prior work with time-resolved (i.e., static) measures of resting-state functional connectivity (FC) may obscure meaningful temporal variation (Hutchison et al., 2013). Dynamic FC (dFC) may provide insight into neural

mechanisms linking ELA to internalizing symptoms by quantifying temporal variability. We examined salience (SN), default mode (DMN), and frontoparietal (FPN) network dFC as a mechanism linking ELA to internalizing severity. Additionally, given prior evidence of sex differences in ELA and in their psychological (Ho et al., 2023) and neurobiological sequelae (Wang et al., 2026), we probed sex differences.
Participants (N = 263; *Mage* = 19.73, *SD*=0.92; *Female* = 185; *Male* = 78) completed an 857-volume resting-state fMRI scan (TR = 0.56 sec). Anxiety and depression severity were clinician-assessed via the Structural Clinical Interview for DSM-5 (First et al., 2016). ELA (threat, deprivation) was assessed via the Child Trauma Interview (Fink et al., 1995). dFC was estimated using an edge time-series to derive SN, DMN, and FPN dwell time and transition frequency. Regression models estimated the associations between ELA and (1) internalizing severity and (2) dFC (covariates: sex, site). Mediation models tested if dFC mediate the associations between ELA and internalizing severity. All analyses were benchmarked against static FC.
Threat was associated with anxiety across the sample (β = .18, p = .004) and in males (β = .26, p = .020). Threat was also associated with depression across the sample (β = .14, p = .036) and in females (β = .21, p = .007). Deprivation was associated with anxiety only in males (β = .24, p = .037) and was unrelated to depression (all ps > .05). ELA did not predict SN, DMN, or FPN dFC (all ps > .05). However, threat was negatively associated with static SN FC across the sample (β = −.20, p = .002), in males (β = −.25, p = .022), and in females (β = −.16, p = .039). Static SN FC did not mediate the association between threat and anxiety (p > .05).
Threat was associated with internalizing severity, but these effects were not explained by SN, DMN, or FPN dFC. Static SN FC may be sensitive to threat, consistent with prior work (Rakesh et al. 2021). However, static SN FC did not explain individual differences in anxiety severity. Analyses revealed heterogeneities in static FC with ELA by sex, supporting prior work (Butler et al., 2025). Thus, ELA is associated with internalizing severity, but may not be explained by dFC.

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Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.16/HH27

Topic: H.06. Anxiety Disorders

Support: MH109991

Title: Deriving Symptom-Specific TMS Targets from Connectivity-Based E-field Modeling in Anxious Misery

Authors: *S. RUEDA[1], S. CHANDRASHEKAR[1], Y. I. SHELINE[2], N. L. BALDERSTON[3]; [2]Psychiatry, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Psychiatry, Univ. of Pennsylvania Deptartment of Psychiatry, Philadelphia, PA

Abstract: Anxious misery is a transdiagnostic cluster of mood and anxiety symptoms spanning depression, anxiety, and trauma-related conditions. Functional MRI (fMRI) in this population has shown distributed dysfunction across default mode, frontoparietal, and salience networks. Transcranial Magnetic Stimulation (TMS) is a promising tool with clinical efficacy for several neuropsychiatric conditions, such as depression and obsessive-compulsive disorder. However, clinical outcomes vary substantially across patients, highlighting the need for personalized protocols informed by patients' symptom profiles and network organization. In this study, we developed a computational pipeline to derive symptom-specific TMS targets from whole-brain resting-state functional connectivity and electrical-field (E-field) modeling. Clinical, structural (T1-weighted MRI), and resting-state fMRI (rs-fMRI) data were drawn from the Dimensional Connectomics of Anxious Misery dataset (N = 118; 64 female, 29 male; mean age 28.29 ± 8.2 years), including 93 transdiagnostic anxious misery patients and 25 healthy controls. Symptom severity was assessed via 17 self-report and 3 clinician-administered measures (e.g., Hamilton Depression Rating Scale and the Neuroticism NEO Five-Factor Inventory). Rs-fMRI data were parcellated, and principal components analysis (PCA) was applied to pairwise connectivity matrices to reduce dimensionality. Components were entered into a lasso regression to identify connectivity features predicting symptom severity, yielding sparse, symptom-specific connectivity weight maps. TMS was simulated using SimNIBS to generate E-field models across 200 cortical sites per participant. E-field maps were then projected onto symptom-weighted networks to estimate post-stimulation symptom change, producing a whole-brain TMS targeting atlas. Our modeling results demonstrate dissociable targeting patterns across symptom dimensions. Anxiety and rumination were best addressed by excitatory protocols in frontal pole/ prefrontal regions and inhibitory stimulation in temporal and occipital cortex, while depression and anhedonia favored excitatory frontoparietal stimulation and inhibitory protocols targeting the frontal pole and temporal gyrus. These findings suggest that symptom heterogeneity within anxious misery maps onto distinct cortical stimulation sites. By integrating individualized connectivity profiles with E-field modeling, this pipeline supports personalized TMS targeting that accounts for network-level heterogeneity and identifies candidate therapeutic targets for future clinical trials.

Disclosures: S. Rueda: None. **S. Chandrashekar:** None. **Y.I. Sheline:** None. **N.L. Balderston:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.17/HH28

Topic: H.06. Anxiety Disorders

Title: A Randomized Controlled Trial of Cannabidiol in Military Personnel with Anxiety Symptoms

Authors: *R. VAN ZIJDERVELD[1], N. LEEN[2], B. BRUINSMA[3], J. M. P. BAAS[4], A. DE WEIJER[5], S. G. GEUZE[6];
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Abstract: Anxiety symptoms occur across a range of psychiatric conditions, including anxiety disorders, posttraumatic stress disorder (PTSD), depression, and attention-deficit/hyperactivity disorder (ADHD). Given prolonged treatment waiting times that often exceed four months, there is a need for interventions that may reduce symptom burden. The endocannabinoid system (eCS) plays a key role in stress regulation and anxiety-related processes, and the lipids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) could therefore serve as a promising pharmacological target. Cannabidiol (CBD), a non-intoxicating phytocannabinoid, facilitates these anxiolytic effects, although evidence in clinical populations remains limited and is often underpowered. In addition, over-the-counter CBD products generally have poor quality, underscoring the need for controlled clinical trials. Therefore, this study examined the effect of standardized CBD administration on anxiety symptoms and stress reactivity in military personnel with PTSD-related or anxiety symptoms. 85 active-duty military personnel and veterans participated in a Phase II clinical double-blind randomized controlled trial and were assigned to receive oral capsules with CBD (200 mg) or a matched placebo three times daily for two weeks. Participants completed Beck's Anxiety Index (BAI) at baseline, one week, and two weeks after initiation. To examine effects on acute stress and recovery, the Maastricht Acute Stress Test (MAST) was conducted at the post-measurement. Subjective stress responses, sleep quality, psychophysiological measures, and endocrine markers from blood plasma were collected and analyzed. Data collection is complete, and full analyses of the RCT will be presented to determine whether CBD has an anxiolytic effect in military personnel with anxiety symptoms and whether it modulates the acute stress response.

Disclosures: R. van Zijderveld: None. **N. Leen:** None. **B. Bruinsma:** None. **J.M.P. Baas:** None. **A. De Weijer:** None. **S.G. Geuze:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.18/HH29

Topic: H.06. Anxiety Disorders

Support: Grant No. BR27198099

Title: Neurofeedback Training for anxiety reduction in students: targeting SMR modulation and frontal alpha asymmetry regulation

Authors: *A. ASHIRBAY[1], G. DATKHABAYEVA[1], A. KUSTUBAYEVA[3], A. ISAGALI[1], M. KULBAYEVA[3], R. BABAYEV[2], R. SHAKHZADAYEV[1], M. KHAIRUSHEV[3], A. DYUSSENBAYEVA[3], S. NESIPBAEV[4], Z. ALTAYEVA[3];
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Abstract: Anxiety is increasingly common among university students, negatively affecting cognitive performance and mental health - making this population a critical target for intervention. Forty students with elevated score on STAI were randomly assigned to a neurofeedback (NFB, n = 20) or sham control group (n = 20) in a single-blind design. Participants completed 10 sessions. The NFB group received feedback based on FAA and SMR spectral power (SP); the sham group received feedback from randomly selected EEG bands. Resting-state EEG was recorded pre-, mid-, and post-course; STAI was assessed pre- and post-intervention. ICA-corrected SMR power, FAA, and STAI scores were analyzed using repeated-measures ANOVA (RM-ANOVA).A significant Day × Group interaction was found for FAA during eyes-closed resting-state EEG ($F = 3.246$, $p = 0.045$). By the end of the course, the NFB group showed increased relative left frontal activity (F3). No significant FAA changes were observed in the sham group. FAA during eyes-open resting-state EEG remained stable across the course in both the NFB and the sham groups. SMR power did not change significantly in either group, though a non-significant trend toward increased SMR SP was noted during eyes-open EEG in the NFB group. RM-ANOVA revealed main effect of Day for STAI scores (F=16.21, $p < 0.001$; F=8.92, $p = 0.005$ for Sate (S) and Trait (T) scales accordingly) but no Day × Group. Bonferroni-corrected post hoc comparisons showed a significant reduction in STAI-S in both groups (all $p < 0.02$). In contrast, STAI-T scores decreased significantly only in the NFB group ($p = 0.021$), while the reduction in the sham group did not reach significance ($p = 0.089$).Overall, NFB training was associated with modulation of resting-state frontal alpha asymmetry rather than robust changes in SMR power. Notably, although training was performed with eyes open, significant FAA changes emerged during eyes-closed resting-state EEG, suggesting that neurofeedback effects may generalize beyond the training condition. Funding. This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. BR27198099).

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Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.19/HH30

Topic: H.06. Anxiety Disorders

Title: Pain Magnification Shows the Strongest Association With Psychological Distress in Temporomandibular Disorders: A Preliminary Study

Authors: *I. ALSHANQITI[1], M. AL-HARTHY[2];
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Abstract: Pain catastrophizing is a multidimensional cognitive-affective construct comprising rumination, magnification, and helplessness. Although elevated catastrophizing has been linked to chronic pain severity, little is known about the relative contribution of individual catastrophizing dimensions to psychological distress and quality of life in Arabic-speaking patients with temporomandibular disorders (TMD). Forty adults diagnosed with TMD according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) completed validated Arabic versions of the Pain Catastrophizing Scale (PCS), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Oral Health Impact Profile-14 (OHIP-14). Correlation analyses were performed to examine relationships between PCS total scores, PCS subdomains, psychological distress, and oral health-related quality of life. Participants had a mean age of 31.2 years, and 25% demonstrated clinically significant catastrophizing (PCS ≥30). Higher PCS scores were associated with greater depressive symptoms (r = 0.42), anxiety symptoms (r = 0.49), and poorer oral health-related quality of life (r = 0.40). Analysis of PCS subdomains revealed distinct patterns of association. Magnification demonstrated the strongest correlations with depression (r = 0.52), anxiety (r = 0.54), and quality-of-life impairment (r = 0.44), exceeding those observed for helplessness and rumination. Helplessness showed moderate associations with depression (r = 0.40), anxiety (r = 0.48), and quality of life (r = 0.38), whereas rumination exhibited comparatively weaker relationships across all outcomes.The association between pain catastrophizing and psychological distress in TMD appears to be driven primarily by the magnification component rather than by rumination or helplessness. These findings suggest that exaggerated threat appraisal of pain may represent a key cognitive-affective mechanism underlying the chronic pain experience in TMD. Targeting pain magnification may provide a more specific therapeutic focus for behavioral interventions aimed at improving psychological well-being and quality of life in patients with TMD.

Disclosures: I. Alshanqiti: None. **M. Al-Harthy:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

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Program #/Poster #: PSTR324.20/HH31

Topic: H.06. Anxiety Disorders

Support: UNIVERSIDAD DEL VALLE DE PUEBLA

Title: Burnout and Psychological Distress in Dental Students: Interactions Between Academic Demands and Socioeconomic Conditions

Authors: *J. M. BRAVO[1], V. HERNÁNDEZ LUNA[2];
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Abstract: Burnout syndrome is a growing mental health concern among healthcare students due to its negative effects on emotional well-being, academic performance, and professional development. Dental students are particularly vulnerable because of the demanding combination of academic workload, clinical training, and continuous evaluation. This study aimed to evaluate the relationship between burnout syndrome and symptoms of depression, anxiety, and stress among undergraduate dental students at a private university in Mexico. A cross-sectional study was conducted in 363 students from different academic semesters. Burnout was assessed using the Maslach Burnout Inventory (MBI), while symptoms of depression, anxiety, and stress were measured using the Depression, Anxiety and Stress Scale (DASS-21). Sociodemographic and academic information was also collected. The findings revealed a high prevalence of psychological distress. Depressive symptoms were present in 70.8% of participants, with 15.2% reporting extremely severe levels. Anxiety was the most prevalent condition, affecting 78.8% of students, while 42.1% presented extremely severe anxiety. Stress symptoms were identified in 68.6% of participants, and 10.5% reached the extremely severe category. Burnout assessment demonstrated elevated levels of emotional exhaustion and depersonalisation, accompanied by lower perceptions of personal accomplishment. Students with higher burnout scores also exhibited greater levels of anxiety, depression, and stress, suggesting a close relationship between emotional exhaustion and psychological distress. These results indicate that a substantial proportion of dental students experience significant emotional burden during their professional training. The coexistence of burnout with anxiety, depression, and stress supports the hypothesis that chronic academic demands may contribute to emotional dysregulation and increased vulnerability to mental health problems. From a neuroscientific perspective, prolonged exposure to academic stressors may affect mechanisms involved in emotional processing and adaptive coping. The findings highlight the importance of implementing mental health screening programmes and preventive interventions aimed at promoting psychological well-being and resilience among future healthcare professionals.

Disclosures: J.M. Bravo: None. **V. Hernández Luna:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.21/HH32

Topic: H.06. Anxiety Disorders

Title: Stress Levels Among Primary Caregivers of Children with Cerebral Palsy at a Comprehensive Rehabilitation Center

Authors: *R. BALTAZAR TELLEZ[1], G. A. ANGELES OCHOA[2], J. ARIAS-RICO[3], E. RAMÍREZ MORENO[4], N. LIBRADO GONZÁLEZ[5], A. ZARAGOZA FERNANDEZ[7], E. MOLINA TRINIDAD[6];
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Abstract: Caregivers of children with cerebral palsy (CP) have a fundamental role in overseeing and fostering the comprehensive development of all physical, emotional, mental, and even social skills, which can lead to burnout, since chronic stress disrupts the nervous system, causing cognitive decline that may manifest as sleep disorders, memory lapses, impaired verbal fluency, or anxiety and depression. The objective of this study was to identify the level of burden among primary caregivers of children with cerebral palsy by applying the ZARIT scale at a Comprehensive Rehabilitation Center. A quantitative, descriptive, exploratory, non-experimental, and cross-sectional study was conducted with a sample of 70 caregivers who had been caring for children with CP for at least one year. The study was approved by the ethics and research committee of the pediatric rehabilitation center where the study was conducted on February 26, 2026. Data were collected using the Zarit Burden Interview (ZBI) by Zarit and Zarit (22 items; Cronbach's α of 0.95), in addition to 7 sociodemographic questions. The results revealed a high proportion of female caregivers, with 63 participants (90%). Fifty-nine percent of the participants has been the primary caregiver for a patient with CP for 5 to 10 years; regarding the level of burden, 67% of caregivers do not experience burden, 26% report mild burden, and 7% report severe burden. The results suggest that the level of caregiver burden among caregivers of children with CP within the pediatric rehabilitation center is low; however, the multidisciplinary team should seek strategies to prevent caregiver burden, as caregivers are exposed to prolonged emotional exhaustion and frustration. This research is descriptive in nature and therefore provides relevant evidence to report on the prevalence of caregiver burnout among caregivers considered "hidden patients," as well as to identify tools for emotional support and education on neurological and psychological symptoms to detect caregiver burnout. The study was conducted without conflicts of interest or external funding.

Disclosures: R. Baltazar Tellez: None. **G.A. Angeles Ochoa:** None. **J. Arias-Rico:** None. **E. Ramírez Moreno:** None. **N. Librado González:** None. **A. Zaragoza Fernandez:** None. **E. Molina Trinidad:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.22/II1

Topic: H.06. Anxiety Disorders

Support: NIMH K01MH12043

Title: Neural Correlates of Day-to-Day Affective Variability: Frontopolar Involvement in Mood and Anxiety Disorders

Authors: *G. DIRUPO[1], P. T. NEUKAM[2], Y. JACOB[2], J. MURROUGH[2], L. S. MORRIS[2,3,4]; [1]Ichan school of Med. at Mount Sinai, New York, NY; [2]Icahn school of Med. at Mount Sinai, New York, NY; [3]Dept. of Exptl. Psychology, Oxford, United Kingdom; [4]Nuffield Dept. of Clin. Neurosciences, Oxford, United Kingdom

Abstract: Psychiatric symptoms are inherently dynamic, yet traditional clinic-based assessments, conducted at long intervals, are prone to inaccuracy due to symptom variability and recall bias. Ecological momentary assessment (EMA) captures this temporal dimension and has the potential to provide insight into symptom variability over time and the individual's ability to regulate affective states. Symptom variability has demonstrated clinical relevance by predicting treatment outcome and depressive worsening. While the structural and functional neural correlates of emotion regulation are well known, less often has this been studied with digital dynamic phenotyping in clinical populations from a transdiagnostic perspective. Symptom variability thus represents not only a behavioral phenotype but a means to investigate the mechanistic behavioral and neural underpinnings of psychiatric disorders. Here, we examine day-to-day variability in anxiety, depression, distress, and motivation and their relationship to emotion regulation brain circuitry in a transdiagnostic sample. Participants with depression and anxiety (DA) disorders (n = 73), and healthy controls (HC; n = 64) completed 30 consecutive days of EMA, rating the daily severity of anxiety, depression, distress, and internal and external motivation on a 0-10 scale via a smartphone application. Day-to-day affective variability was quantified independently for each metric using the root mean square of successive differences (RMSSD), an estimate of affective/behavioral instability or lability. High-resolution 7-Tesla structural MRI data were available for a subsample of participants (DA = 39; HC = 20). Between-group differences in mood instability were examined using two-sided Mann-Whitney U tests, and partial correlations assessed associations between affective instability and volumes of a priori selected ROIs based on their relevance to affective regulation, controlling for sex, age, and estimated total intracranial volume (FDR corrected). Results indicated that EMA compliance did not differ between groups. RMSSD was higher in DA compared to HC across both symptom (anxiety, distress, depression), and psychological (internal/external motivation) domains, suggesting that not only symptom intensity but also impairment in regulating symptoms is a central problem for patients transdiagnostically. Greater day-to-day variability in anxiety was associated with smaller cortical volume in emotion regulation-relevant ROIs, but mean anxiety

level was not, suggesting neurobiological underpinnings specific to instability rather than symptom severity.

Disclosures: G. Dirupo: None. **P.T. Neukam:** None. **Y. Jacob:** None. **J. Murrough:** None. **L.S. Morris:** None.

Poster

PSTR324: Anxiety Disorders: Preclinical and Human Studies, Mechanisms, and Interventions

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR324.23/II2

Topic: H.06. Anxiety Disorders

Support: McNair Scholar Program

Title: Social Identity Concealment Predicts Challenging Aspects of the Psychedelic Experience

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Abstract: Classic psychedelics (e.g., psilocybin, LSD, DMT, mescaline), which act as 5-HT2A receptor agonists, have shown promise as part of treatment for mood disorders, given their ability to induce neuroplasticity. However, the psychedelic experience is profoundly shaped by context, expectations, and interpersonal relationships, also known as set-and-setting. For marginalized populations, the set-and-setting of a psychedelic experience is complicated by social and environmental stressors. A hypervigilant state resulting from identity concealment may hinder the neurophysiological process of structural plasticity, increasing susceptibility to challenging trip experiences. The present study evaluated whether minority stress and identity concealment predicted challenging and mystical aspects of the psychedelic experience among marginalized participants. We hypothesized that higher minority stress and identity concealment would predict more challenging experiences. In a cross-sectional survey, 27 participants (33% multiracial, 33% white, 15% Latino, 11% Asian, 7% other races; 56% women; 52% LGBQA+) reported on either their most recent or salient psychedelic experience (93% recreational). Pearson correlations tested how minority stress—measured using the Trauma Symptoms of Discrimination Scale —and identity concealment—via the Quinn Active Concealment Scale —predicted acute psychological dynamics captured by the Challenging Experience Questionnaire (e.g., paranoia, isolation) and Mystical Experience Questionnaire (e.g., transcendence, positive mood). Participants who scored higher on identity concealment reported significantly more paranoia during their psychedelic experience. Similarly, participants who reported more minority stress characterized by uncontrollable hyperarousal reported more paranoia, yet also more transcendence, during their psychedelic experience. Our findings suggest that social masking around stigmatized aspects of identity may be linked with distress, specifically paranoia, during a psychedelic experience. However, paranoia may co-exist with transcendent aspects of the

experience for those with marginalized identities. These findings may help professionals who provide psychedelic-assisted therapy for marginalized populations provide culturally competent care that acknowledges the potential for psychedelic experiences to include both distressing and transformative aspects.

Disclosures: A.A. Figueroa: None. **K.L. Goldey:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.01/II3

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH Grant R01MH133846
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Title: Dissecting Region- and Sex-Specific Roles of Sapap3 Across Cortico-Striatal Circuits in Compulsive-Like Behavioral Phenotypes

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Abstract: Obsessive-compulsive disorder (OCD) is associated with dysfunction within cortico-striato-thalamo-cortical (CSTC) circuitry, yet the molecular mechanisms within specific CSTC regions that regulate behavioral control remain poorly defined. Sapap3 (DLGAP3), a postsynaptic scaffolding protein enriched in dendritic spines, is the most extensively studied monogenic model of OCD and has served as a major platform for mechanistic and therapeutic studies for nearly two decades. However, global *Sapap3* knockout models cannot distinguish region-specific molecular function from developmental adaptations associated with lifelong gene deletion. Here, we tested whether localized *Sapap3* knockdown within discrete CSTC regions produces dissociable behavioral phenotypes.
Adult male and female C57BL/6 mice received bilateral AAV9-mediated delivery of *Sapap3*-targeting shRNA or scrambled control shRNA into the lateral orbitofrontal cortex (lOFC) or caudoputamen (CPu). Behavioral testing began five weeks post-infusion and included open field, elevated zero maze (EZM), splash groom, dig test, marble burying, nestlet shredding, and object-in-place assays. Knockdown efficacy was verified by Western blot analysis of targeted tissue micropunches in separate behaviorally naïve cohorts.
Sapap3 protein expression was significantly reduced in targeted tissue relative to contralateral control tissue (paired t-test, n=8 pairs, p=0.014). Behavioral effects were region- and sex-

dependent. In males, CPu knockdown increased EZM risk assessment frequency (p=0.0328), time in risk assessment (p=0.0016), and head-dip behavior (p=0.0159), and increased splash-groom duration (p=0.0205). In contrast, male lOFC knockdown increased grooming latency in the splash test (p=0.0037). Female lOFC knockdown increased grooming bout duration (p=0.0372) and decreased digging latency (p=0.0095). Multiple behavioral measures were unaffected, indicating selective behavioral alterations across domains.
These findings demonstrate that *Sapap3* function is neither uniform across CSTC circuitry nor across sexes and instead produces dissociable region- and sex-dependent behavioral phenotypes. Together, these data suggest that localized molecular perturbations within discrete CSTC regions differentially regulate behavioral control and establish a region-specific framework for investigating synaptic mechanisms and emerging OCD-relevant risk genes within cortico-striatal circuitry. These findings provide critical context for interpreting nearly two decades of OCD-relevant mechanistic inference derived from global *Sapap3* knockout models.

Disclosures: U.R. Chatterjee: None. **M.E. Cahill:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.02/II4

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: Blick Scholars Fund, VCU
R01DA058958
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P30DA033934
R00DA045795

Title: Dysregulating brain transposable elements to study stress-induced social deficits

Authors: *C. SMITH[1], N. L. TRUBY[2], J. L. BELL[2], P. J. HAMILTON[2];
[2]Neurosci. and Anat., [1]Virginia Commonwealth Univ., Richmond, VA

Abstract: Chronic stress drives risk for developing neuropsychiatric disorders including major depressive disorder and post-traumatic stress disorder, and social dysfunction is often cited by patients with these disorders as a key impediment to quality of life. The molecular mechanisms underlying social withdrawal following chronic stress are not currently well-understood, but our lab has previously identified transposable element (TE) escape in medial prefrontal cortex (mPFC) as a mechanism through which social deficits can be induced in stress-naïve mice. In addition, reanalyzing published RNA-sequencing data from mice who underwent chronic social defeat stress (Bagot et al., 2017) in the mouse mPFC revealed that stress resilient mice exhibit a

more dynamic TE transcript down-regulation pattern than susceptible mice compared to unstressed controls. Thus, we hypothesize that TE dysregulation is also a mechanism through which stress-induced social deficits emerge, and that these deficits can be reversed by improving the brain molecular mechanisms that control TE expression. To test this, we employed three synthetic variants of the transcriptional cofactor TRIM28, which endogenously represses TEs. TRIM28 variants are delivered via viral-mediated gene transfer to the mPFC of adult male and female C57BL/6J mice. The TRIM28 variants each exert distinct TE transcriptional control: $TRIM28^{WT}$ mimics the endogenous transcriptional repressor of TEs, $TRIM28^{VPR}$ is a transcriptional activator of TEs, and $TRIM28^{NFD}$ binds endogenous TRIM28's binding partners but exhibits no transcriptional activity. We delivered TRIM28 variants or a GFP control to mice prior to or following a chronic social stressor and performed a battery of social and stress-related behavioral assays. Stress susceptibility was assessed in a Social Interaction (SI) Test, with stress susceptible being defined with SI ratio less than one and stress resilient defined as SI ratio greater than one. All TRIM28 variant groups contained both susceptible and resilient mice. No TRIM28 variant significantly impacted non-social behaviors in either susceptible or resilient mice. In the Three Chamber Social Recognition Task, susceptible and resilient mice were differentially impacted by TRIM28 variants, with mPFC $TRIM28^{WT}$ specifically improving social deficits in susceptible mice. Taken together, these results indicate that mPFC TE transcript expression is stratified by social phenotypic response to stress, and that repressing mPFC TEs improves pro-social behavior in response to chronic stress.

Disclosures: C. Smith: None. **N.L. Truby:** None. **J.L. Bell:** None. **P.J. Hamilton:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.03/II5

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: UKRI MRC Grant MR/Z504737/1
Boehringer Ingelheim support

Title: Characterising sleep in a rat model of post-traumatic stress disorder using continuous 28-day wireless recordings across multiple cortico-limbic structures

Authors: D. ANDERSON[1], A. WILLIAMS[1], L. K. PRITCHARD[1], D. TITHERADGE[1], R. H. WILLIAMS[2], M. W. JONES[1], E. N. CAHILL[1], ***R. J. PURPLE**[1];
[1]Sch. of Psychology & Neurosci., Univ. of Bristol, Bristol, United Kingdom; [2]CNS, Boehringer Ingelheim, Biberach, Germany

Abstract: Introduction: Traumatic experiences are common, yet only a minority of individuals develop post-traumatic stress disorder (PTSD), indicating marked variability in vulnerability.

Sleep after trauma is thought to regulate emotional memory processing, but the sleep and circuit changes accompanying trauma exposure remain poorly defined. We refined a PTSD model incorporating genetic background, early-life stress, and adult trauma, using longitudinal wireless electrophysiology to characterise pre- and post-trauma sleep and cortico-limbic dynamics. Methods: Lewis rats (N=27; 15 females) were maternally separated from postnatal days 1-14 or reared under standard conditions. In adulthood, rats were implanted with four local field potential electrodes in four of six regions: infralimbic cortex (IL), prelimbic cortex, basolateral amygdala (BLA), bed nucleus of the stria terminalis, dorsal CA1, and ventral CA1. Electrodes were connected to a Neurologger (TSE Systems) for continuous wireless home-cage recording across a 28-day protocol. Rats were exposed to predator threat odour (bobcat urine, cat fur, and conspecific blood) or neutral odour (acetophenone) in a conditioned place preference paradigm. Additional measures included ultrasonic vocalisations, faecal corticosterone metabolites, acoustic startle, elevated plus maze, light-dark box, and open field testing. Results: Preliminary results indicate that predator threat exposure (PTE) induced persistent anxiety-like phenotypes in a subset of animals, including avoidance of the odour-paired context, increased startle, and reduced exploration in anxiety assays. PTE was associated with an acute reduction in total sleep time compared with neutral odour exposure. Across the following week, this was accompanied by increased REM sleep fragmentation, reduced BLA theta-band activity (5-10 Hz), and reduced broadband IL-BLA coherence. Discussion: These findings suggest that PTE produces enduring behavioural alterations consistent with a PTSD-like phenotype, alongside sustained changes in sleep architecture and cortico-limbic network activity. Ongoing analyses will leverage the full longitudinal dataset to identify sleep, neuroendocrine, developmental, and circuit-level predictors of individual vulnerability to trauma.

Disclosures: D. Anderson: None. **A. Williams:** None. **L.K. Pritchard:** None. **D. Titheradge:** None. **R.H. Williams:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim. **M.W. Jones:** None. **E.N. Cahill:** None. **R.J. Purple:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boehringer Ingelheim.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.04/II6

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: VA Merit l01 BX004626
NIH NINDS RO1 NS073899

Title: Effects of FKBP51 ablation in stress-related disorders

Authors: *B. A. ARIZA[1,2], D. MEZQUITE-GARCIA[1,2], L. J. BLAIR[1,3,2];
[1]Dept. of Mol. Med., Univ. of South Florida, Tampa, FL; [2]Byrd Alzheimer's Ctr. and Res. Inst., Tampa, FL; [3]James A. Haley Veterans' Hosp., Tampa, FL

Abstract: Stress-related disorders, including post-traumatic stress disorder and depression, remain major contributors to global disease burden. The 51 kDa FK506-binding protein (FKBP51), a co-chaperone of Heat Shock Protein 90 (Hsp90) and regulator of glucocorticoid signaling, has emerged as a promising target for stress-related disorders due to its involvement in stress responsivity and neuropsychiatric disease vulnerability. This project investigates whether FKBP51 reduction promotes resilience against stress-associated phenotypes and evaluates approaches for therapeutic targeting of FKBP51. The effects of FKBP51 deletion were assessed in FKBP51 knock-out (KO) mice following chronic stress susceptibility and stress-associated behaviors. In parallel, antisense oligonucleotide (ASO)-based approaches targeting FKBP51 were developed and evaluated to assess target engagement and knockdown efficiency *in vitro*. Here, we test the hypothesis that reducing FKBP51 expression will promote resilience to maladaptive responses to chronic stress exposure. Together, this study aims to evaluate FKBP51 as a therapeutic target and establishes gene-targeting approaches for modulating stress-related pathways.

Disclosures: B.A. Ariza: None. **D. Mezquite-Garcia:** None. **L.J. Blair:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.05/II7

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: U.S. Department of Defense Grant

Title: EphrinA4 Mimetic Peptide Attenuates Fear Memory and Offers a Novel Therapeutic Strategy for PTSD

Authors: B. POPIK, M. DINES, F. SHHADE, ***R. LAMPRECHT**;
Univ. of Haifa, Haifa, Israel

Abstract: Post-traumatic stress disorder (PTSD) is characterized by persistent traumatic memories, highlighting the need for interventions that target the underlying mechanisms of memory formation and persistence. We previously developed pep-ephrinA4, an ephrinA4-mimetic peptide that inhibits EphA4 signaling and disrupts fear memory consolidation and reconsolidation following systemic administration. In the present study, we optimized its therapeutic potential by comparing administration routes, evaluating safety, and determining the durability of its effects on fear memory. Rats received pep-ephrinA4 or an inactive control peptide via intravenous (IV), subcutaneous (SC), or intranasal (IN) administration at multiple

doses. Peptides were administered either 1 hour after auditory fear conditioning to target memory consolidation or 30 minutes before memory reactivation to target reconsolidation. Fear memory was assessed by conditioned freezing behavior. Intranasal delivery produced a significant attenuation of conditioned fear memory. Notably, a single intranasal administration following fear conditioning or before memory reactivation resulted in long-lasting reductions in fear expression, with significant effects persisting for at least one week and treatment-related differences remaining detectable one month after administration. Safety assessment following intranasal delivery revealed no adverse clinical signs, gross pathological abnormalities, or clinically meaningful alterations in hematological, biochemical, or coagulation parameters. These findings identify intranasal delivery as the optimal route for pep-ephrinA4 administration and demonstrate that a single administration of pep-ephrinA4 can produce durable reductions in fear memory without detectable toxicity. The results support further development of pep-ephrinA4 as a targeted therapeutic strategy for attenuating pathological traumatic memories associated with PTSD.

Disclosures: B. Popik: None. **M. Dines:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **F. Shhade:** None. **R. Lamprecht:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.06/II8

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Investigation of Boldine Effects on Stress Resilience and Decision-Making in Maternal Separation and Social Isolation-Induced Early-Life Stress in Female Wistar Rats via Modulation of the 5-HT3R/BDNF-FOXO1 Pathway

Authors: *L. AKOTKAR[1], U. ASWAR[2], P. KALE[2];
[1]Dept. of Pharmacology,, Poona Col. of Pharmacy, Pune India, Pune, India; [2]Dept. of Pharmacol., Poona Col. of Pharm., Pune, India

Abstract: Stress-related neuropsychiatric disorders are strongly associated with adverse early-life experiences, including maternal separation (MS) and social isolation (SI), which impair stress resilience, emotional regulation, and cognitive function. Boldine (BDN), a natural aporphine alkaloid with antioxidant, anti-inflammatory, and neuroprotective properties, was evaluated for its effects on stress resilience and decision-making in a female Wistar rat model of early-life stress. Female Wistar rats were divided into six groups (n=6/group): normal control (NC), stress control (MS+SI), fluoxetine (FLX, 5 mg/kg, i.p.), and BDN-treated groups (5, 10,

and 15 mg/kg, i.p.). Behavioural assessments included the Sucrose Preference Test, Hole Board Test, and Novel Object Recognition Test. Biochemical analyses comprised corticosterone, BDNF, glutamate, and GABA estimation, while GR, 5HT3, BDNF, and FOXO1 gene expression and histopathological changes in the hippocampus, amygdala, and medial prefrontal cortex were evaluated. MS+SI exposure significantly induced anhedonia, anxiety-like behavior, and cognitive impairment, evidenced by reduced sucrose preference, decreased exploratory activity, and impaired recognition memory (###$p<0.001$ vs NC). Stressed animals also exhibited elevated corticosterone levels, neurotransmitter imbalance, altered GR, 5HT3, BDNF, and FOXO1 expression, and marked neuronal degeneration in stress-sensitive brain regions (###$p<0.001$). BDN produced dose-dependent improvements, with the 10 and 15 mg/kg doses significantly improving behavioral performance and restoring biochemical and molecular alterations ($p<0.05$-0.001 vs stress control). Histopathological analysis confirmed attenuation of stress-induced neuronal damage. These findings suggest that BDN enhances stress resilience and improves decision-making by modulating neuroplasticity, neurotransmitter balance, and HPA-axis dysfunction, highlighting its therapeutic potential in stress-related neuropsychiatric disorders.

Disclosures: L. Akotkar: None. **U. Aswar:** None. **P. Kale:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.07/II9

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Escalating, Reorganizing, and Synchronizing: Sex-Divergent Defensive Dynamics During Chronic Social Defeat Stress

Authors: *P. ONTIVEROS-ANGEL, M. OLIVEIRA DAVID, Y. GROSSMAN, D. DUMITRIU;
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Abstract: Chronic social defeat stress (CSDS) is a widely used model of stress susceptibility, yet the behavioral dynamics of defeat in females and sex differences in coping strategies remain poorly understood. We developed a sex-inclusive CSDS paradigm in which male and female C57BL/6J mice were concurrently exposed to an aggressive CD1 and continuously scored across defeat sessions (days 1, 9, and 11; n = 39). Defeat behaviors were analyzed using linear mixed-effects models and principal component analysis, with p-values corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate (reported as q); post-defeat social avoidance was assessed using the social interaction (SI) test.Freezing was the predominant defensive behavior in both sexes, accounting for more than 80% of scored time. Nevertheless, males exhibited greater freezing ($q = 0.002$) and more defensive fighting than females (fight duration $q = 0.010$; frequency $q = 0.012$). Importantly, coping strategies diverged across repeated

defeat. A significant Sex × Day interaction was observed for freezing ($q = 0.031$), with males showing a steeper increase from day 1 to day 11 ($p = 0.021$), whereas females increasingly occupied corner zones (Cliff's $d = -0.47$, $p = 0.037$). At the multivariate level, behavioral profiles were sex-distinct on days 1 and 11 but transiently converged on day 9. Behavioral organization remained stable across late defeat sessions in males (day 9-11, $r = 0.75$), whereas females exhibited continued behavioral reorganization.Following defeat, females displayed robust social avoidance, spending significantly more time in corner zones during the target-present phase of the SI test ($p = 0.004$), whereas defeated males did not exhibit significant social avoidance ($p = 0.09$). We next tested whether repeated co-exposure to social defeat promoted dyadic behavioral synchrony between male-female pairs. Initially, partner freezing showed no detectable association, but by day 11 a significant correlation had emerged ($r = 0.58$, $p = 0.035$) that persisted after controlling for aggression received (partial $r = 0.59$, $p = 0.033$), consistent with the emergence of dyadic behavioral synchrony. Together, these findings demonstrate that chronic social defeat elicits sex-specific trajectories of behavioral adaptation while promoting emergent dyadic behavioral synchrony during repeated shared stress.

Disclosures: P. Ontiveros-Angel: None. **M. Oliveira David:** None. **Y. Grossman:** None. **D. Dumitriu:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.08/II10

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: National Institutes of Health T32-MH125786
McLean Lorenz Pope Fellowship
Dupont Warren Award

Title: Early-life social stress drives lasting behavioral deficits that are reversed by positive social interaction in adulthood

Authors: *C. MIDDLETON[1], M. G. KEARNEY[3], B. WASSERMAN[2], K. J. RESSLER[4]; [1]Ressler Lab. Div. of Depression and Anxiety, McLean Hosp., Boston, MA; [2]McLean Hosp., Concord, MA; [3]McLean Hospital, Harvard Med. Sch., Belmont, MA; [4]Harvard Med. Sch., McLean Hosp. / Harvard Med. Sch., Belmont, MA

Abstract: Early-life social adversity increases the risk for severe psychiatric disorders, including depression, anxiety, and PTSD. Furthermore, repeated chronic stress during sensitive developmental periods alters emotional regulation and stress reactivity by impairing the ability to discriminate between threat and safety signals. Although the extinction of non-social fear is well-established in classical conditioning procedures. How social fear, specifically social fear learned

in early life, may be extinguished remains an unknown but critical question. Here, we observed using a juvenile chronic social defeat stress paradigm in C57BL/6J mice that social avoidance deficits could be rescued by employing repeated social exposure in adulthood. Through this approach, we demonstrate the potential for positive social interactions in adulthood to drive social fear extinction following early life social stress. Juvenile male C57BL/6J mice were defeated by adult male Swiss Webster CFW aggressors across five consecutive days during the juvenile period (P28-P32). In adulthood, early life defeated animals underwent a five-day social exposure protocol in which they were introduced to novel, nonaggressive CFW mice under a cup in an open-field arena. Open-field social interaction tests, before and after exposure, were performed to evaluate the social interaction ratio, assessing social fear and avoidance. We observed that juvenile social defeat produced robust and lasting social avoidance into adulthood. Positive social exposure significantly reduced social avoidance and is consistent with an extinction-like process, whereas a sham exposure without a social partner led to unchanged social avoidance. Further, a consolidated exposure in which mice received a single prolonged exposure (100 minutes) did not lead to the successful extinction of social fear. Together, these findings establish a novel social fear extinction procedure after early life social defeat to provide evidence that repeated positive social interventions in adulthood can selectively buffer the lasting consequences of early-life adversity. Importantly, this work carries translational relevance for uncovering neural mechanisms enabling social-based recovery from fear and stress-related disorders secondary to early life trauma.

Disclosures: C. Middleton: None. **M.G. Kearney:** None. **B. Wasserman:** None. **K.J. Ressler:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: National Institutes of Health T32-MH125786 (MGK)
McLean Lorenz Pope Fellowship (MGK)
Dupont Warren Award (MGK)

Title: Social deep learning approaches to quantify social fear and extinction after early life trauma

Authors: *B. S. WASSERMAN[1], C. MIDDLETON[2], M. G. KEARNEY[3], K. J. RESSLER[4]; [1]McLean Hosp., Belmont, MA; [2]Ressler Lab. Div. of Depression and Anxiety; McLean Hosp., Boston, MA; [3]McLean Hospital, Harvard Med. Sch., Belmont, MA; [4]Harvard Med. Sch., McLean Hosp. / Harvard Med. Sch., Belmont, MA

Abstract: Early life trauma is associated with the development of persistent social fear, a leading independent risk factor for suicide, and a significant contributor to numerous psychiatric disorders including Posttraumatic Stress Disorder (PTSD). Notably, early life and social trauma are risk factors for resistance to pharmacological and psychological therapies. How positive social experiences in adulthood can modify social fear behaviors learned in early life remains a critical question. Here we investigate how early life social trauma in the form of juvenile Chronic Social Defeat Stress (jCSDS) alters naturalistic adult social behaviors and whether positive social interaction in adulthood can rescue naturalistic adult social behaviors. Specifically, we employ a deep learning approach utilizing SLEAP (Social LEAP Estimates Animal Poses), as part of a workflow to quantify naturalistic social behaviors after early life social trauma and with and without a social exposure therapy. We observe that early life social defeat trauma dramatically alters adult social behaviors in C57/BL6J mice that experienced juvenile Chronic Social Defeat Stress (jCSDS), 5 days of aggressive encounters with a CFW mouse. Specifically, we observe significant changes in social approach, avoidance, and freezing in naturalistic home cage interactions compared with control mice that did not receive early life jCSDS. We then examined how positive social experience in the form of a social exposure vs a sham exposure without any social partner present alters social behaviors. We find that social exposure but not a sham exposure leads to a significant reduction in aberrant social behaviors (approach, avoidance, and freezing) and we correlate the social interaction parameters during the social exposure with final test of social behavior to identify predictive factors for the successful extinction of social fear.

Disclosures: B.S. Wasserman: None. **C. Middleton:** None. **M.G. Kearney:** None. **K.J. Ressler:** Other; KJR has performed scientific consultation for Bioxcel, Bionomics, Acer, Takeda, and Jazz Pharma; serves on Scientific Advisory Boards for Sage and the Brain Research Foundation; has received sponsored.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR325.10/II12

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: VA CDA2 Grant BX006528

Title: Adolescent Social Defeat Stress Alters Neuroimmune and Structural Markers in a Sex-Specific Manner

Authors: *C. PEI[1], E. E. HISEY[2,1];
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Abstract: Adolescence is a sensitive developmental period during which early-life trauma can produce lasting alterations in neural development and long-term health outcomes. Although

neural mechanisms underlying stress-related disorders have been widely studied, the cellular processes driving persistent pathology remain unclear. Increasing evidence suggests that chronic neuroimmune dysregulation may contribute to long-term disruptions in brain homeostasis following stress exposure. To investigate the neuroimmune consequences of adolescent stress, we used an adolescent chronic social defeat stress (aCSDS) mouse model. We performed immunohistochemical analyses at both early post-defeat (P35) and adult (P70) timepoints. Tissue was stained for ionized calcium-binding adaptor molecule 1 (IBA-1), a microglial marker; myelin basic protein (MBP), a marker of myelination; and the pro-inflammatory cytokines TNF-α and IL-1β. We aimed to determine: (1) whether adolescent social defeat produces persistent chronic inflammatory changes, (2) which cellular mediators contribute to these effects, and (3) which brain regions are disrupted following stress exposure. Previous work from our lab demonstrated decreased prelimbic cortex (PL) axonal innervation within the basolateral amygdala (BLA) following adolescent defeat stress, with male-specific reductions also observed in the nucleus accumbens (NAc). In the present study, we identified a sex-specific decrease in MBP expression within the prefrontal cortex (PFC) of male, but not female, mice following aCSDS. These myelination deficits correlate with previously observed male-specific behavioral impairments in sociability, suggesting a potential relationship between altered myelination and stress-induced behavioral outcomes. Notably, reductions in MBP and axonal innervation occurred independently of overt microglial activation, suggesting that a classical microglia-mediated inflammatory response may not drive these changes. Future directions are focused on characterizing inflammatory signaling in female mice, determining how immune-related changes influence neural circuitry, and identifying structural alterations associated with stress exposure, including potential changes in BLA morphology between defeated and control animals. Together, these findings support a sex-specific effect of adolescent social defeat stress on myelination and neural connectivity and suggest that non-canonical inflammatory mechanisms may contribute to long-term stress-related pathology.

Disclosures: C. Pei: None. **E.E. Hisey:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: grant MH053851 from the National Institute of Mental Health

Title: The Medial Prefrontal Cortex-to-Lateral Septum Pathway Mediates the Therapeutic Effects of Fear Extinction on Stress-Induced Coping Deficits

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Abstract: Background Post-traumatic stress disorder (PTSD) and other stress-related psychiatric illnesses are characterized by maladaptive avoidance behaviors and shifts toward passive coping strategies under threat. Although fear extinction serves as a primary mechanism for trauma-focused exposure therapies, the precise neural circuits underlying their ability to restore adaptive, active coping behaviors following chronic stress remain poorly understood. **Methods** Using extinction learning as a rodent model of exposure therapy, adult male and female Sprague-Dawley rats were subjected to chronic unpredictable stress (CUS) following initial fear conditioning or exposure to tones without shock (Tone Controls). Following CUS, all rats were subject to an extinction session comprised of 16 tones without shock. The therapeutic effects of fear extinction on active versus passive coping behavior were evaluated 24 hours later using the shock-probe defensive burying (SPDB) test. Dual-virus chemogenetic strategies, combining AAVrg-hSyn-eGFP-Cre in the lateral septum (LS) plus DIO-hM4D(Gi), DIO-hM3D(Gq) or mCherry control in the infralimbic (IL) subregion of ventromedial prefrontal cortex (vmPFC), were utilized to selectively inhibit or activate neurons projecting from IL to the LS during extinction (for the Gi DREADD) or in place of extinction (for the Gq DREADD). **Results** Chronic stress significantly impaired active coping on the SPDB test, decreasing bury ratios and elevating immobility time. Extinction reversed these CUS-induced deficits, reinstating active burying behavior. Chemogenetic Gi-DREADD inhibition of the IL-LS pathway during extinction prevented its therapeutic benefits, blocking the recovery of active burying and leaving stress-induced passive immobility intact. Conversely, direct Gq-DREADD activation of the IL-LS pathway in stressed, non-extinguished animals significantly increased the bury ratio, partially mimicking the behavioral recovery achieved via natural extinction learning. **Conclusions** These findings demonstrate that the IL-LS circuit is necessary for the beneficial effect of fear extinction in reversing the stress-induced shift from active coping to passive coping. While direct activation of this specific projection is sufficient to partially drive adaptive behavioral recovery, full therapeutic efficacy likely requires a coordinated network across broader prefrontal cortical circuits. Further, targeting vmPFC-LS pathway activity might be a promising adjunctive approach to enhance the clinical efficacy of cognitive behavioral therapies for stress-induced psychiatric disorders.

Disclosures: J. Liu: None. **D.A. Morilak:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR325.12/II14

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: RF1NS135548
R01AG081874

Title: Testicular Photobiomodulation Attenuates PTSD-like Fear Memory Dysregulation and Cognitive Impairment in Mice

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Abstract: Background: PTSD is associated with persistent fear memories, impaired extinction, and cognitive dysfunction. Although most interventions directly target the brain, peripheral organs may influence stress-related behavioral outcomes through systemic endocrine, metabolic, and immune signaling. Here, we tested whether testicular photobiomodulation could attenuate PTSD-like behavioral impairments in mice.Methods: 3-months-old male mice received 1064-nm continuous-wave testicular photobiomodulation for 5 min in combination with restraint stress. Fear acquisition, tone and context recall, repeated extinction, and Y-maze spontaneous alternation were used to assess PTSD-like memory and cognitive phenotypes. Transcriptomic profiling was performed to explore molecular changes induced by photobiomodulation.Results: In fear memory tests, restraint stress altered tone- and context-associated fear responses, whereas testicular photobiomodulation partially normalized PTSD-like memory abnormalities. During repeated extinction testing, photobiomodulation-treated mice showed reduced tone-evoked freezing at the later extinction phase, suggesting improved extinction of conditioned fear. In the Y-maze test, photobiomodulation enhanced spontaneous alternation without changing total arm entries, indicating improved working memory independent of locomotor activity. Transcriptomic profiling revealed distinct gene expression patterns between restraint and photobiomodulation-treated mice, suggesting potential molecular adaptations related to stress regulation, metabolic homeostasis, and neuroimmune modulation.Conclusion: Testicular photobiomodulation attenuates PTSD-like fear memory dysregulation and cognitive impairment in mice. These findings support peripheral photobiomodulation as a novel non-brain-targeted strategy for modulating trauma-related behavioral abnormalities.

Disclosures: P. Zou: None. **Z. Huang:** None. **Y. Zhang:** None. **J. zhang:** None. **X. zong:** None. **Q. Zhang:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR325.13/II15

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: DGAPA-PAPIIT IN 225 925
DGAPA-PAPIME PE 305 125

Title: The effect environmental enrichment on females exposed to predator scent stress

Authors: *P. TORRES-CARRILLO[1], K. JULIO HERNÁNDEZ[1], D. GARCÍA-OCAMPO[1], S. APARICIO-HUERTA[1], J. DELGADO SUASNAVAR[1], E. RIVERO TERRONES[1], D. B. PAZ-TREJO[2], H. SANCHEZ-CASTILLO[3];
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Abstract: Stress is a major risk factor for psychiatric disorders, cognitive impairments and alterations in pain sensitivity. Women remain highly underrepresented in preclinical stress research regardless of evidence for heightened HPA axis reactivity, greater vulnerability to chronic stress-induced depressive-like behaviors, and distinct neuroendocrine stress response. Predator scent stress (PSS) engages innate fear circuits and triggers robust neuroendocrine and behavioral responses. Research in environmental enrichment (EE) shows anxiolytic, antidepressant-like and pro-cognitive effects, suggesting EE may buffer deleterious consequences of stress. In order to characterize how multimodal EE attenuates behavioral sequelae of PSS (10 minutes exposition to lynx urine), we evaluate 40 female Wistar rats (12 weeks old) in 4 groups (control, PSS, EE, and PSS+EE). EE items, simultaneously presented 2 times per day, were social (housing with conspecifics), structural (shelters and gnawing materials), nutritional (dietary variety including novel foods), and cognitive enrichment (novel objects and foraging challenges). Tests were elevated zero maze (EZM), novel object recognition (NOR), saccharine preference (SP), and tail flick (TL). PSS significantly increased tail withdrawal latency in TF, indicating stress-induced hyperalgesia. Lower values for PSS+EE suggests that EE effectively prevents hyperalgesia. PSS significantly reduced time spent in open arms in EZM, reflecting high anxiety-like behavior. EE showed a robust anxiolytic effect by increasing time in open arms of PSS+EE which also showed a significant reduction in risk assessment behaviors compared to control. Stress impaired the initial engagement with novelty in NOR while enrichment normalized exploration deficits. Discrimination index scores showed a trend toward improvement in the PSS+EE group relative to PSS. Results in SP indicate that PSS did not induce a robust anhedonia-like phenotype. Our findings demonstrate that a multimodal EE protocol exerts major protective effects against PSS-induced behavioral alterations in female Wistar rats. EE effectively attenuated thermonociceptive hypersensitivity, anxiety-like behavior, and stress-induced exploratory deficits, without negatively affecting hedonic state. Data highlight the importance of including female subjects in preclinical stress research and support the translational relevance of EE as a non-pharmacological strategy for mitigating consequences of stress.

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Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: I01BX003890I

Title: Elucidating susceptibility to a PTSD-like phenotype in female rats

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Abstract: Post-Traumatic Stress Disorder (PTSD) develops following emotional trauma that results in sustained emotional stress and functional impairment. While men experience trauma more frequently, women suffer from PTSD at twice the rate. Rodent models of PTSD also show sex differences. Also, not everyone that experiences a trauma will develop PTSD, suggesting there are individual susceptibilities. Previously, we developed a rat model to identify PTSD susceptibility in male rats (RISP-M). Due to sex differences in behavioral phenotypes in anxiogenic conditions, i.e. male rats engage in freezing behavior and females engage in anxioescapic behavior, we could not assume the RISP-M model would apply to females. We hypothesized that female rats would have different criteria that reveal susceptibility to PTSD than male rats. Furthermore, we hypothesized that lavage procedure to monitor the estrus cycle may impact classification criteria. Additionally, we evaluated neuronal plasticity using *Arc* and *Homer1a* (*H1a*) mRNA expression in resilient (Res) and susceptible (Sus) female rats before and during trauma to test if Sus female rats have altered neuronal plasticity within the prefrontal cortex (PFC), hippocampus, and amygdala systems. We hypothesized that all three regions would have alterations in Sus females, compared to Res, and these differences would be different from those observed in males. Specifically, we hypothesize that Sus females will have a higher percentage of neurons with *Arc/H1a* expression in the basolateral amygdala immediately after trauma, compared to Res females. In male rats there were no observed differences within the basolateral amygdala. We report that RISP-M criteria do not predict susceptibility to PTSD-like symptoms in female rats. However, female rats can be classified as Sus or Res using the combination of their responses to a mild stressor and anxiety-like behavior in the elevated plus maze (RISP-F). Additionally, we found that the lavage procedure significantly changes the behavior of female rats causing them to engage in more anxioescapic behavior compared to non-lavaged females. Lastly, we report differences between Res and Sus female rats in neuronal plasticity of the PFC, hippocampus, and amygdala before and during trauma. This reveals functional differences that are associated with individual susceptibility. These findings introduce a reliable sex-specific model of susceptibility to a PTSD-like phenotype in female rats, which will allow us to further explore sex differences within PTSD and generate translatable approaches for building resilience in people with PTSD.

Disclosures: K. Denney: None. **A.I. Vazdarjanova:** None.

Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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Title: Network signature for PTSD-like pathology

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Abstract: Current research on post-traumatic stress disorder (PTSD) heavily relies on isolated behavioral metrics, lacking a syndrome-level characterization. By coupling stress-enhanced fear learning (SEFL) with screening across four PTSD-like symptomatic domains, we identified a distinct PTSD-susceptible subpopulation exhibiting phenotypes relevant to avoidance, negative mood, hyperarousal, and intrusive memory. Unbiased whole-brain activity mapping resolved the functional architecture of PTSD-like pathological network, identifying the primary motor cortex (M1) as a hub. Mechanistically, the emergence of PTSD-susceptible network is driven by suppression of M1 neuronal activity, alongside a downregulation of dopamine D2 receptors

(D2R) . Remarkably, conditional knockout of M1 D2R alone was sufficient to recapitulate PTSD-like behaviors. Pharmacological activation of M1 via chemogenetic method or by chronic administration of D2R agonist successfully ameliorated behavioral abnormalities. This behavioral rescue was independent of locomotor enhancement, suggesting a motor-indepent fucntion of motor cortex in regulating PTSD-like behaviors.Collectively, these findings uncover a non-motor role for M1 as a vital hub in PTSD pathophysiology, demonstrating that direct modulation or targeted D2R pharmacology holds profound therapeutic potential for treating syndromic PTSD.

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Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

Location: WCC Halls A-C

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: T32 NS082145
#BX004693
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Title: Characterization of 5-HT2A Receptor Agonists on Dopamine Neuron Activity in the Ventral Tegmental Area: Implications for Stress-Related Disorders

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Abstract: Post-traumatic stress disorder (PTSD) affects millions of individuals in the United States. Despite this, current pharmacological and behavioral treatment options often result in high relapse and limited remission. Neurobiologically, PTSD is associated with hypofrontality in the medial prefrontal cortex (mPFC), a deficit that impairs top-down regulation and contributes to core symptoms of hypervigilance and emotional dysregulation. Due to the lack of sufficient treatment options, 5-HT2A receptor agonists, also classified as serotonergic psychedelics, have emerged as a promising intervention capable of producing rapid, sustained symptom reduction by restoring neural plasticity. Emerging clinical evidence suggests promising therapeutic effects; however, the mechanisms driving these outcomes and associated plasticity remain unclear. Most psychedelics research has focused on serotoninergic and cortical signaling, but recent evidence suggests that dopamine may act as a neuromodulator in psychedelic-induced plasticity. Accordingly, this project aims to characterize the impact of psychedelics on dopamine system function, specifically investigating how 5-HT2A receptor agonists affect dopamine neuron activity through mPFC-dependent circuits in the ventral tegmental area (VTA). Using *in vivo*

extracellular electrophysiology, we measured spontaneously active dopamine neuron activity, firing rate, and burst firing following the administration of three agonists for 5-HT2A receptors: DOI, TCB-2, and NBOH. We found that all three compounds significantly increased the number of spontaneously active dopamine neurons in the VTA, with minimal changes to firing rate or bursting patterns. To investigate the necessity of cortical input, we injected TTX into the mPFC following psychedelic administration. Interestingly, while the previously increased dopamine population activity returned to baseline in animals treated with DOI and TCB-2, the effects of NBOH persisted despite mPFC inactivation. These results suggest that while the mPFC is a key regulator of psychedelic-induced dopaminergic activity in the VTA, high-affinity ligands may engage additional pathways to modulate activity and plasticity throughout the brain. To validate these findings in a translationally relevant model, we used single prolonged stress and observed that DOI successfully returned stress-induced elevations in VTA dopamine activity back to baseline. Ultimately, these data provide critical insight into the potential for psychedelics to rescue stress-induced circuit dysfunction.

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Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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Pennsylvania Department of Health (4100095613; 3)

Title: Therapeutic Efficacy of Psilocybin Demonstrates Context-Dependence in a Rat Model of Post-Traumatic Stress Disorder.

Authors: *C. N. ZAWATSKY[1], C. MORAN-BARISO[1], A. SIPE[1], J. E. NYLAND[2]; [1]Pennsylvania State Univ. Col. of Med., Hershey, PA; [2]Neural and Behavioral Sci., Penn State Col. of Med., Hershey, PA

Abstract: Clinical imaging studies and preclinical investigation evidence that the increased rate and severity of chronic pain among individuals with post-traumatic stress disorder (PTSD) are due to trauma-induced neuroplastic changes in the nucleus accumbens (NAc). Accordingly, therapies that enhance neuroplasticity in the NAc may provide therapeutic benefits in chronic pain comorbid with PTSD by attenuating trauma-induced changes. Here, we tested the therapeutic efficacy of the neuroplasticity-enhancing agent, psilocybin, for trauma-induced anxiety and mechanical allodynia using a well-established animal model of PTSD. We hypothesized that psilocybin's therapeutic mechanism involves mitigating trauma-induced

changes in the NAc by enhancing oxytocin-mediated neuroplasticity. We employed the single prolonged stress (SPS) in rats, a favored preclinical PTSD model due to its capacity to reliably induce a phenotype that satisfies all DSM-5 and model validity criteria. Critically, SPS also induces pain sensitivity in rats. The therapeutic efficacy of psilocybin intervention was evaluated using well-defined behavioral assays of anxiety and pain sensitivity, and psilocybin-induced NAc molecular changes were assessed by qPCR. Findings indicate that rats receiving psilocybin in a social context (1 hour of human handling) demonstrated greater reductions in trauma-induced changes in anxiety and allodynia metrics compared to rats that received psilocybin without social interaction. Gene expression analysis indicates that social interaction modulates psilocybin-induced changes in gene expression in the NAc. Future directions using a chemogenetic approach will test whether oxytocinergic projections from the paraventricular nucleus to the NAc are required for psilocybin's therapeutic efficacy, and how social interaction relates to this pathway. These results will provide translational evidence of the therapeutic mechanism of psilocybin for PTSD and comorbid pain. Such data will enhance our understanding of the treatment of PTSD and its comorbidities and may aid in the design of novel therapeutic approaches for this debilitating pathology with inadequate treatment options.

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Poster

PSTR325: Post-Traumatic Stress Disorder and Other Psychiatric Disorders: Preclinical Models

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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Title: Electroacupuncture treatment for PTSD: Restoring glutamatergic and glymphatic homeostasis to alleviate PTSD-like behaviors

Authors: J. HAN, H. PARK, ***M. CAI**;
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Abstract: Ju Eun Han, Hee Ra Park, Mudan Cai*
Post-traumatic stress disorder (PTSD) is a mental disorder that develops following exposure to traumatic events. Given the limited response and remission rates associated with selective serotonin reuptake inhibitors, the current first-line pharmacological treatment for PTSD, alternative therapeutic strategies are needed. In the present study, we investigated the effects of electroacupuncture (EA) at the GV29 (Yintang) acupoint administered three times per week for 2

weeks in a mouse model of PTSD induced by single prolonged stress and shock (SPSS). EA treatment significantly ameliorated anxiety and cognitive impairment and normalized serum corticosterone and serotonin levels in SPSS-exposed mice. Furthermore, EA reduced hippocampal glutamate levels and the expression of glutamatergic signaling-related proteins. EA also attenuated neuronal activity and normalized the number of dendritic spines in the hippocampus, as assessed by Golgi staining. Consistent with these findings, EA significantly reduced glutamate-induced excitotoxicity, as evidenced by the regulation of apoptosis-related signaling pathways. To further elucidate the underlying mechanisms, we investigated whether glymphatic dysfunction contributes to PTSD pathology and whether EA modulates glymphatic function in association with glutamatergic regulation. EA restored glymphatic homeostasis-associated markers and improved glymphatic clearance. These changes were accompanied by reduced neuronal dysfunction and enhanced neural plasticity in brain regions involved in fear processing. Taken together, our findings suggest that EA exerts therapeutic effects on PTSD through coordinated regulation of glutamatergic neurotransmission and glymphatic function, providing novel insight into the neurobiological mechanisms underlying electrical stimulation-mediated recovery from traumatic stress.
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Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Microcircuits of the Prelimbic Cortex Across the Estrous Cycle

Authors: *V. NUDELL, A. SICHER, N. CROWLEY;
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Abstract: Circulating estrogen (E2) has been found to impact brain regions that control executive behaviors such as risk taking, decision making and reward seeking. However, it is not known how E2 acts on the mechanistic level in prefrontal circuits to modulate these behaviors. Here, I assessed modulation of intrinsic excitability and action potential dynamics of pyramidal (PYR) and somatostatin (SST) neurons in the prelimbic (PL) cortex using whole cell patch clamp electrophysiology. Male and female transgenic (SST:Ai9) mice were taken from their home cage the day of recording and vaginal cytology was collected from females at the time of brain

harvest. Female estrous stages were grouped into low E2 (metestrus/diestrus) and high E2 (proestrus/estrus). Electrophysiology measurements, combined with sex and estrous stage, were assessed using linear mixed effects modeling including the random effects of age, litter, and cage. Comparison of resting membrane potential (RMP) revealed no significant difference in RMP of PYR or SST cells across groups. Rheobase and action potential threshold did not show any significant differences between hormonal states. Action potential half-width was significantly lower in high E2 females compared to both low E2 females ($p=0.0416$) and males ($p=0.0242$). Fast after-hyperpolarization was similar across groups in each cell type. Repeated firing was similar between groups in PYR and SST neurons, with no voltage-dependent effects revealed by repeated measurements of clamping cells at -70 mV. Ongoing experiments are evaluating spontaneous post-synaptic currents of PYR and SST neurons across the estrous cycle to assess how differential hormonal activity impacts this network. This detailed electrophysiological characterization provides a strong basis to define the impact of the estrous cycle on the PLC.

Disclosures: V. Nudell: None. **A. Sicher:** None. **N. Crowley:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

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Program #/Poster #: PSTR326.02/II22

Topic: H.08. Drugs of Abuse and Addiction

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Stavros Niarchos Foundation (SNF) Precision Psychiatry Seed Grant
New York Nutrition & Obesity Research Council Pilot and Feasibility Grant

Title: Decoding brain-wide signatures and behavioral dynamics of alcohol withdrawal using two-timepoint activity labeling

Authors: *R. SETARA[1,2], E. J. KYZAR[1,3], M. EISENGART[2,4], S. VIRKAR[2,4], C. D. SALZMAN[2];
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Abstract: Developing effective treatments for alcohol use disorder (AUD) requires untangling the neural processes underlying withdrawal. Brain regions do not function in a vacuum; withdrawal and associated behaviors are likely mediated by large-scale, brain-wide coordination of activity. However, widely used methods for measuring network-wide dynamics across the brain (such as single-timepoint cFos immunohistochemistry) lack sensitivity and are prone to noise and variability. To overcome these limitations, we employ a two-timepoint neural activity labeling with subtraction (TTP-S) approach to isolate and quantify overlapping patterns of alcohol withdrawal at distinct timepoints. We applied this approach to a cohort of mice exposed

to different withdrawal trajectories. One group underwent alcohol withdrawal at both timepoints (withdrawal-withdrawal, WW group; n = 5) following a two-bottle choice consumption of 10% alcohol or water. A second group experienced withdrawal followed by acute re-exposure to alcohol (withdrawal-ethanol, WE group; n = 5) using the same paradigm. Compared to cFos staining alone, our TTP-S method demonstrated significantly higher sensitivity in identifying neural populations active during alcohol withdrawal. Whole-brain analysis revealed over 100 regions consistently activated during withdrawal, including ensembleswithin the central amygdala that are strikingly negatively correlated with other significantly-activated regions. Additionally, our design enabled the identification of brain networks containing separate, intermingled neuronal populations differentially activated in withdrawal versus intoxication within the WE cohort, which potentially mediate the behavioral switch between these states. We also leveraged DeepLabCut for automated behavioral phenotyping during withdrawal in the elevated plus maze and open field test, and we correlated these behavioral measures directly with whole-brain activation patterns. Together, this approach successfully integrates whole-brain activity mapping with behavioral assays to elucidate how alcohol withdrawal and re-exposure shape motivated behavior through distinct patterns of neural ensemble activation.

Disclosures: R. Setara: None. **E.J. Kyzar:** None. **M. Eisengart:** None. **S. Virkar:** None. **C.D. Salzman:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR326.03/II23

Topic: H.08. Drugs of Abuse and Addiction

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American Heart Association 25PRE1369483

Title: Homeostatic scaling of cortical inhibition and disinhibition confers functional resiliency against acute alcohol effects

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Abstract: Prefrontal cortical function depends on a balance between excitatory and inhibitory signaling. Studies in reduced preparations indicate that acute alcohol enhances GABAergic inhibition and suppresses NMDA receptor-mediated excitation, predicting an overall reduction in cortical activity. To test this hypothesis in vivo, we used cell-type-specific two-photon calcium imaging to examine the effects of acute alcohol on neuronal activity in the anterior cingulate cortex (ACC) of awake mice. Contrary to expectations, acute alcohol produced minimal changes in pyramidal neuron activity while significantly reducing activity in parvalbumin (PV) and somatostatin (SST) interneurons. Given the tight coupling between excitation and inhibition in

cortical circuits, these findings suggest that reductions in inhibitory activity may compensate for alcohol-induced suppression of excitatory signaling, thereby preserving pyramidal neuron activity. Vasoactive intestinal polypeptide (VIP) interneurons, which preferentially inhibit other inhibitory neurons and promote disinhibition of pyramidal cells, exhibited a modest decrease in overall activity but increased population-level synchrony following alcohol exposure. Optogenetically mimicking synchronous VIP activation enhanced ACC network activity, supporting a role for alcohol-induced VIP synchronization in maintaining pyramidal neuron activity. Consistent with this interpretation, systemic muscarinic receptor antagonism blocked alcohol-induced VIP synchrony and unmasked suppressive effects of alcohol on a subset of pyramidal neurons. Together, these findings demonstrate that alcohol differentially affects cortical interneuron populations and suggest that coordinated reductions in inhibition and increased disinhibition confer resilience to the suppressive effects of alcohol within intact prefrontal cortical circuits.

Disclosures: Y. Ko: None. **M. Saunders Lucy:** None. **V. Mamillapalli:** None. **R. Huda:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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NIH Grant P60AA007611

Title: Activating prefrontal parvalbumin-expressing interneurons reduced impulsive choice dependent on sex and strain.

Authors: *K. G. BRYANT[1], S. T. COOK[1], J. WORRELL[1], A. REMES[2], N. J. LAROCHE[1], T. BONKO[1], E. R. IHRKE[1], C. C. LAPISH[1];
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Abstract: Impulsivity has been identified as both a risk factor for and consequence of drug and alcohol use disorders and is indeed the strongest known phenotypic predictor of these disorders. Impulsivity is highly heritable, but multifactorial, which makes it critical to pin down the overall neurobiological changes underlying this behavior instead of trying to identify specific genetic targets. The alcohol-preferring “P” rat is a validated rodent model of familial risk for excessive drinking that innately exhibits the same impulsive phenotype that is observed in humans with a family history of substance use. GWAS studies have repeatedly identified changes in cortical, inhibitory interneuron signaling as a key predictor of substance use severity, supporting that

inherited interneuron dysfunction may contribute to addiction vulnerability. The present study sought to determine whether cortical parvalbumin-expressing (PV) inhibitory interneuron function was innately modified in P rats, and whether activating PV interneurons was sufficient to reduce impulsive choice. Male and female Wistars (control strain) and P rats were injected with a virus expressing either an excitatory DREADD receptor (hM3Dq) or control protein (dTom). Rats were then trained on a Delay Discounting (DD) task where animals had to choose between a larger, delayed reward vs. a smaller, immediate reward. Following training through all of the delays (0, 1, 2, 4, 8, and 16s), DREADD manipulations occurred during the delays where the choice between the immediate and delayed option is most difficult (4 and 8s). Our results uncovered that the effects of PV activation depended on strain and sex, such that it reduced impulsive choice in female Wistars and male P rats only. Furthermore, the effects of PV activation were primarily concentrated at the beginning of the DD session, suggesting that cortical PV interneuron function may be most critical in the early phase of DD. When investigating innate difference in PV function, it was revealed that P rats have reduced perineuronal net (PNN) coverage on cortical PVs as compared to Wistars. PNNs preferentially form around PVs and are critical for their activity and function. These findings showed that P rats exhibit innate differences in PV functional markers that could underlie increased impulsive choice, and that activating PVs is sufficient to reduce impulsive choice, though this depends on sex and strain. A greater understanding of the cortical cell types which regulate impulsivity and are altered as a result of genetic risk can help uncover novel targets for addiction vulnerable populations.

Disclosures: K.G. Bryant: None. **S.T. Cook:** None. **J. Worrell:** None. **A. Remes:** None. **N.J. LaRoche:** None. **T. Bonko:** None. **E.R. Ihrke:** None. **C.C. Lapish:** None.

Poster

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Program #/Poster #: PSTR326.05/II25

Topic: H.08. Drugs of Abuse and Addiction

Support: Ekam Imaging Inc.

Title: The ethanol paradox: dose-dependent, non-linear changes in global brain activity and functional connectivity: A BOLD fMRI study in awake rats

Authors: D. ATHREYA[1], B. AXE[2], N. CAVALLARO[1], A. MOORE[3], R. J. ORTIZ[5], ***P. P. KULKARNI**[2], C. F. FERRIS[4];
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Abstract: Ethanol is one of the most widely consumed psychoactive substances, yet its acute dose-dependent effects on whole-brain activity and functional connectivity remain incompletely characterized. Here we used pharmacological functional MRI (phMRI) to map real-time changes in brain activity in response to linear-increasing doses of ethanol in fully awake rats. Using a within-subjects Latin square design, male and female Sprague-Dawley rats (N = 12) received intraperitoneal injections of vehicle (saline) or ethanol (1, 2, or 3 g/kg; 16% w/v in saline) during imaging on a 7T Bruker MRI. Changes in blood oxygen level-dependent (BOLD) signal were recorded over a 30-minute window following injection. Resting-state functional connectivity (rsFC) data were collected around 35 minutes post-injection. All data were registered to a 3D rat brain atlas with 169 segmented brain areas, enabling site-specific quantification of brain activation and connectivity changes. Blood alcohol concentration (BAC) was measured 30 minutes post-injection using a spectrophotometric ethanol assay and confirmed dose-proportional increases across treatment groups. Ethanol produced complex, dose-dependent changes in BOLD signal that diverged from simple neural suppression. Lower doses (1 g/kg) decreased positive BOLD signaling and increased negative BOLD responses, consistent with the pharmacological literature on acute ethanol exposure. Higher doses (2-3 g/kg) unexpectedly increased positive BOLD signals and attenuated negative BOLD responses, potentially reflecting ethanol's known vasodilatory properties and enhanced cerebral blood flow. Resting-state functional connectivity also demonstrated a U-shaped dose-dependent curve, with the medium and high doses producing the greatest reduction in global connectivity. Specific brain regions including the thalamus, hippocampus, piriform cortex, sensory cortex, and cerebellum displayed this response, showing correlation to ethanol's neuromodulatory effects. These findings provide the first comprehensive dose-response characterization of ethanol's effects on global brain activity and functional connectivity in awake, unanesthetized rats and establish a foundation for understanding alcohol's acute neuromodulatory mechanisms.

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Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: H.08. Drugs of Abuse and Addiction

Support: PHS U01AA025481
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Title: Investigating the effect of chronic alcohol use on locus coeruleus integrity of rhesus macaques

Authors: *C. TEVES[1], L. R. LURYE[2], R. KHADKA[2], V. C. CUZON CARLSON[2], K. GRANT[2], E. M. VAZEY[1];
[1]Biol., Univ. of Massachusetts Amherst, Amherst, MA; [2]Oregon Natl. Primate Res. Ctr., Oregon Hlth. and Sci. Univ., Beaverton, OR

Abstract: Studies across species have shown a bidirectional relationship between heavy alcohol consumption and cognitive impairments, including cognitive inflexibility. Studying the underlying cellular mechanisms that contribute to alcohol-induced cognitive inflexibility is important to finding therapeutic targets. The locus coeruleus (LC) brainstem nucleus is critical for cognitive flexibility. LC neurons are highly metabolically active, making them particularly vulnerable to cellular mechanisms that can be disrupted by chronic alcohol use. We hypothesized that chronic alcohol use disrupts LC integrity which contributes to cognitive inflexibility in alcohol use disorder. Young adult rhesus macaques (6-7 years) performed an attentional set-shift task (ASST), measuring cognitive flexibility, before and after undergoing an open access ethanol drinking paradigm (22 hrs/day) for 180 days. Alcohol-naïve controls were given isocaloric maltodextrose during the open access paradigm. Macaques were characterized as low (n=6) or high (n=9) cognitive performers based on their performance in the ASST. Animals were also categorized based on their daily volitional ethanol intake: control (alcohol-naïve) (n=12), low (n=8) (<3 g/kg), or heavy (n=7) (≥3 g/kg for ≥20% of days) drinkers. Brainstem tissue containing LC was acquired via the Monkey Alcohol Tissue Research Resource from Oregon National Primate Research Center. Quantitative histology was performed to measure tyrosine hydroxylase+ LC neurons, hyperphosphorylated tau (ptau), and 4-HNE, an oxidative stress marker in the LC. Preliminary results show comparable LC neuronal counts across drinking and cognitive performance categories among macaques that underwent the open access ethanol paradigm. In alcohol-exposed monkeys, we found ptau positive neurons within LC and higher oxidative stress in heavy drinking female macaques. Our results show neuropathological changes within LC of alcohol drinking macaques at a young age despite no overt neuronal loss. Future experiments include measuring markers of neuroinflammation, which has been shown to be a consequence of chronic alcohol use and has been correlated with cognitive impairment. These translational studies will contribute to our understanding of how alcohol impacts critical cognitive nodes within the brain.

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Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Stavros Niarchos Foundation (SNF) Precision Psychiatry Seed Grant
New York Nutrition & Obesity Research Council Pilot and Feasibility Grant

Title: 4-hydroxytamoxifen (4-OHT) leads to avoidance of paired stimuli and activates an aversive brain-wide neuronal ensemble

Authors: *M. EISENGART[1,2], S. VIRKAR[1,2], E. J. KYZAR[1,3], R. SETARA[1], C. D. SALZMAN[1];
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Abstract: 4-hydroxytamoxifen (4-OHT), a selective estrogen receptor modulator, is commonly used to drive expression of genetic and viral constructs in rodent models. Experiments in our lab have shown that a single dose of 4-OHT appears to cause a lasting reversal of alcohol preference in two bottle free-choice (2BFC) tasks in multiple mouse strains. To examine if this effect is alcohol specific, we performed a sucrose preference assay; mice receiving 4-OHT compared to vehicle showed a significant decrease in sucrose preference. To determine whether 4-OHT causes a conditioned avoidance response, a conditioned taste aversion (CTA) test was performed using a Kool-Aid (KA) solution. 4-OHT caused a dramatic drop in KA preference in the traditional CTA paradigm where the tastant is novel. Surprisingly, even with previous exposure to KA, 4-OHT still caused a stark CTA. We then performed a conditioned place avoidance (CPA) test to determine whether the aversive effect of 4-OHT generalized beyond tastants. We found a significant decrease in time spent in the 4-OHT-paired compartment compared to the vehicle compartment.Taken together, we inferred that 4-OHT activates an aversive ensemble in the brain. To test this hypothesis, we used a CNS-targeting viral vector expressing a Cre-dependent activating DREADD (Gq), and following viral expression, administered 4-OHT in the homecage in Trap2 mice. Then, a CTA was performed using the novel tastant paradigm previously described, followed by an injection of CNO to activate the 4-OHT homecage ensemble. Compared to controls, Gq+CNO mice had a reduced preference for KA. Thus, investigators should carefully account for potential aversive effects when using 4-OHT. However, when combined with techniques used to tag active ensembles, 4-OHT can be a valuable tool to map neural networks of devaluation and avoidance. For example, we employed two-timepoint neural activity labeling with subtraction (TTP-S) to quantify overlapping patterns of neural activation during alcohol devaluation at distinct timepoints. TTP-S revealed over 150 regions activated by alcohol devaluation, including a large cortico-amygdalar network with many brain areas implicated in aversive conditioning. In conclusion, 4-OHT has been demonstrated to be deeply aversive across multiple behavioral paradigms, and researchers should account for these effects in experimental designs.

Disclosures: M. Eisengart: None. **S. Virkar:** None. **E.J. Kyzar:** None. **R. Setara:** None. **C.D. Salzman:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Title: Region and Sex Dependent Effects of Alcohol Binge Drinking on Prefrontal Somatostatin Neural Activity and Brain Hemodynamics Across Arousal States

Authors: *J. A. FLORES[1], M. HOSSAIN[2], D. GREENAWALT[3], P. J. DREW[4], N. A. CROWLEY[5];
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Abstract: Sleep is linked to large arterial dilations that increase cerebral blood volume (CBV) in the cortex. It is believed that these vascular changes help to remove waste from the brain by periarterial pumping of cerebrospinal fluid, and disruption of this process is implicated in neurodegenerative disorders and cognitive decline. Alcohol binge drinking can negatively impact sleep, natural hemodynamic fluctuations, and cortical somatostatin (SST) neural activity. Here, we investigated the effects of alcohol on SST neurons and CBV in the prefrontal cortex (PFC) during sleep. To provide a regional comparison, we also collected data from the barrel cortex (S1BF). We combined voluntary binge alcohol consumption or control conditions using the Drinking in the Dark (DID) paradigm with measurements of calcium activity via fiber photometry and behavioral tracking in head-fixed male and female SST-IRES-Cre mice. Our main goal was to understand the relationship between SST and CBV signals across arousal states and how alcohol binge drinking disrupts these potentially interacting signals. Our data shows that binge alcohol consumption reduced stimulus-evoked SST activity across binge drinking days in females but not in males, and CBV response was unaffected in both sexes. Additionally, 4 weeks of voluntary alcohol consumption through the DID model reduced SST activity during REM sleep in females but not in males. Interestingly, REM-related CBV responses may also be altered, with a decrease observed in females and an increase in males. These findings highlight a link between alcohol consumption, PFC SST neurons, and REM sleep-related hemodynamic changes, providing a potential neural locus of action of binge alcohol consumption-induced deficits on sleep and neural function. Gaining a deeper understanding of these interactions could

inform the development of targeted strategies to address sleep disturbances caused by substance misuse, providing promising therapeutic targets for alcohol use disorder.

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Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Topic: H.08. Drugs of Abuse and Addiction

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Stavros Niarchos Foundation (SNF) Precision Psychiatry Seed Grant
New York Nutrition & Obesity Research Council Pilot and Feasibility Grant

Title: Lasting devaluation of alcohol by the selective estrogen receptor modulator 4-hydroxytamoxifen (4-OHT)

Authors: *S. VIRKAR[1,2], M. EISENGART[1,2], E. J. KYZAR[2,3], R. SETARA[2,4], C. D. SALZMAN[2];
[1]Barnard Col., New York, NY; [2]Zuckerman Inst., New York, NY; [3]New York State Psychiatric Inst., New York, NY; [4]Columbia Univ., New York, NY

Abstract: Understanding the neural mechanisms underlying alcohol preference is critical to developing new treatment strategies for alcohol use disorder (AUD). Most behavioral paradigms studying alcohol-seeking behavior have relied on devaluation procedures that change the qualities of alcohol as a stimulus (e.g., quinine adulteration), which limits the translatability of these results to clinical populations. The drug 4-hydroxytamoxifen (4-OHT) is commonly used to drive expression of genetic and viral constructs in rodent models. In a pilot experiment, we aimed to examine brain-wide activation during alcohol consumption in a two bottle free-choice (2BFC) 10% EtOH paradigm using Trap2:Ai14 (TrAi) mice. Surprisingly, when 4-OHT (50 mg/kg) was administered during EtOH access, there was a lasting reversal in alcohol preference in both males and females. When this paradigm was repeated in C57BL6/J mice, a single dose of 4-OHT led to a decrease in alcohol preference that lasted for 1-2 weeks compared to vehicle-treated mice. To simulate binge drinking while still assaying choice, we used a 2BFC paradigm with intermittent 3hr access to 20% EtOH. 4-OHT similarly caused a decrease in alcohol preference compared to vehicle in this binge consumption model. Importantly, this lasting alcohol devaluation continues days after it is no longer pharmacologically available. We then sought to explore the pharmacologic mechanism of 4-OHT-mediated alcohol devaluation. 4-OHT is a selective estrogen receptor modulator with high affinity for estrogen receptor alpha (ERa), and whole-brain activity mapping studies performed in our lab have identified brain regions active in alcohol devaluation that express high levels of estrogen receptors (i.e., arcuate

nucleus and medial preoptic area of the hypothalamus). Therefore, we treated mice with an injection of a specific estrogen receptor antagonist (i.e., to ERa or ERb) followed by a 4-OHT injection in a 2BFC paradigm to define the receptor dependencies of this drug-induced alcohol devaluation. Taken together, 4-OHT appears to alter the relationship between the animal and the value of alcohol as a stimulus, rather than altering the stimulus itself, providing a new paradigm to explore how animals value alcohol.

Disclosures: S. Virkar: None. **M. Eisengart:** None. **E.J. Kyzar:** None. **R. Setara:** None. **C.D. Salzman:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Program #/Poster #: PSTR326.10/II30

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH K99AA029169
MizzouForward Undergraduate Research Training Grant

Title: Executive control and reward circuitry gray matter volume differences as a function of alcohol use disorder risk factors in emerging adults

Authors: *M. GUTIERREZ[1], R. U. COFRESI[2];
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Abstract: Alcohol use disorder (AUD) is a major contributor to disability and premature mortality rates worldwide. Low alcohol sensitivity and polysubstance use are important risk factors for heavy drinking and AUD, yet their neuroanatomical correlates remain underexplored. Recent structural magnetic resonance imaging (MRI) studies suggest that variation in gray matter volume (GMV) within executive control and reward-related brain circuitry may contribute to differences in AUD vulnerability. This study examined the associations between GMV and alcohol-related risk factors in young adult drinkers. Participants were 67 healthy adults (21-25 years; 48% female and 52% male) from the University of Missouri community who reported at least one binge-drinking episode within the past three months. T1-weighted anatomical brain scans were acquired on a 3T Siemens Prisma MRI scanner and processed using CAT12 within SPM12 in MATLAB. Multiple linear regression models examined associations between regional GMV, alcohol sensitivity, and substance co-use, controlling for total intracranial volume, age, sex, and body mass index. Alcohol sensitivity was measured using the Alcohol Sensitivity Questionnaire (ASQ). Substance co-use was defined as participants who, in addition to alcohol use, reported nicotine and/or cannabis use in the past year. Lower sensitivity to alcohol's intoxicating effects was associated with lower GMV in the anterior orbital gyrus (B= .105, p=.007) and middle cingulate gyrus (B= .168, p=.027). In contrast, substance co-use was

associated with greater GMV in the medial orbital gyrus (B= .206, p=.003), thalamus (B= .285, p=.016), putamen (B=.171, p=.019), frontal pole (B= .155, p=.031), and anterior orbital gyrus (B= .068, p=.046) compared to alcohol-only use. Distinct AUD risk factors were associated with dissociable neurostructural patterns in young adults. Lower alcohol sensitivity was linked to reduced GMV in orbitofrontal and cingulate regions implicated in executive control and behavioral regulation, while substance co-use was associated with greater GMV in frontostriatal regions involved in reward processing and incentive salience. These findings suggest that vulnerability to AUD and problematic alcohol use may arise through partially distinct neuroanatomical pathways during emerging adulthood. Moreover, increased GMV within reward-related circuitry may reflect a neurobiological risk phenotype rather than neurotoxic consequences of chronic substance exposure.

Disclosures: M. Gutierrez: None. **R.U. Cofresi:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

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Program #/Poster #: PSTR326.11/II31

Topic: H.08. Drugs of Abuse and Addiction

Title: Individualized dACC-MFG Target Localization Reveals Altered Functional Connectivity in Alcohol Use Disorder

Authors: *Y. BAO, H. ZHOU, Y. HU;
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Abstract: Background: Alcohol use disorder (AUD) is a major public health problem. Transcranial magnetic stimulation (TMS) has emerged as a potential neuromodulatory intervention for AUD, but individualized targets based on intrinsic functional connectivity remain insufficiently characterized. **Objective:** This exploratory resting-state functional MRI study aimed to characterize dorsal anterior cingulate cortex (dACC)-guided individualized middle frontal gyrus (MFG) targets in AUD and to examine their clinical relevance. **Methods:** 56 male participants meeting AUDIT-based criteria for AUD (Alcohol Use Disorders Identification Test [AUDIT] ≥8; age 40.55±9.12 years) and 61 male healthy controls (age 37.56±8.86 years) were included; age did not differ significantly between groups. No TMS or other neuromodulatory intervention was administered. Based on resting-state functional MRI data, individualized TMS targets were computed using a refined seed-based functional connectivity approach. Specifically, the dACC was used as the seed region, and the MFG location showing the strongest positive functional connectivity with the dACC was identified for each participant as the individualized TMS target. We assessed target spatial distribution, target-to-dACC connectivity, whole-brain voxel-wise connectivity, and associations with AUDIT scores within the AUD group. **Results:** Compared with controls, the AUD group showed significantly weaker connectivity between the individualized MFG target and dACC (t=2.945,

p=0.004). By contrast, dACC connectivity with conventional scalp-based targets did not differ between groups, including the F3 target (t=0.420, p=0.675) and 5-cm rule target (t=1.105, p=0.271). Within the AUD group, AUDIT scores were positively correlated with individualized target-to-dACC connectivity (r=0.344, p=0.009), indicating that greater alcohol-use severity was associated with stronger dACC-MFG coupling. No significant correlations were observed for the F3 target (r=-0.141, p=0.298) or 5-cm rule target (r=-0.047, p=0.732).

Disclosures: Y. Bao: None. **H. Zhou:** None. **Y. Hu:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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NIH P50AA017823
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AHA 24PRE1201066

Title: Adolescent alcohol consumption disrupts adult whole-brain resting state functional connectivity and behavioral outcomes in mice

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Abstract: Adolescent alcohol exposure is associated with negative behavioral outcomes later in life, including adult heavy alcohol use. Complex changes in functional networks across cortical and subcortical regions are likely to be involved in the heightened risk of psychiatric disorders seen with adolescent alcohol use. Here, we examined whole brain resting state functional connectivity, intrinsic excitability of pyramidal neurons in key reward-related brain regions, and behavioral outcomes in adults after adolescent binge-like drinking in mice. Male and female C57BL/6J mice consumed alcohol or water in a drinking-in-the-dark (DID) paradigm throughout adolescence (PND 29-54) and were tested for brain or behavior changes 30 days after cessation of DID. Generalized linear modeling (GLM) was used to assess sex and alcohol effects while accounting for cohort and litter effects. Functional magnetic resonance imaging revealed sex-specific changes in whole-brain resting state functional connectivity with particularly pronounced disruptions in connections between the prefrontal cortex and the striatum. Patch clamp electrophysiology experiments in the infralimbic cortex, basolateral amygdala, and anterior insular cortex are ongoing. However, preliminary evidence has demonstrated region- and sex-specific changes in the intrinsic excitability of excitatory pyramidal neurons, suggesting

that intracellular mechanisms governing the excitability of pyramidal cells likely contribute to observed global changes in functional connectivity. We also found that adult females, and not males, exhibited aversion-resistant alcohol consumption after adolescent alcohol exposure (n=9-11, p=0.04). We hypothesize behavioral deficits may also be linked sex-specific changes in neuronal excitability and whole-brain functional connectivity. Future work will more thoroughly examine female vulnerability to adolescent alcohol use.

Disclosures: L. Seemiller: None. **H. Unsal:** None. **Y. Xie:** None. **A. Sicher:** None. **M. Hossain:** None. **P.J. Drew:** None. **N. Zhang:** None. **N.A. Crowley:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR326.13/JJ1

Topic: H.08. Drugs of Abuse and Addiction

Support: Grant no. 81571305
Grant no. 82171487

Title: Disrupted cortical functional gradients in Alcohol Use Disorder

Authors: *S. LU, Y. HU, T. HONG;
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Abstract: Background: Alcohol use disorder (AUD) is associated with widespread alterations in functional connectivity and large-scale network organization. However, most previous work has treated functional networks as discrete modules, leaving unclear whether AUD affects the continuous cortical hierarchy linking primary perception and transmodal cognition. **Objective:** This study examined whether AUD alters cortical functional gradients and the geometry of large-scale functional networks in low-dimensional gradient space. **Methods:** We analyzed baseline resting-state fMRI data from 81 patients with AUD during early abstinence (5-12 days) and 61 age-matched healthy controls. Diffusion map embedding was used to derive cortical functional connectivity gradients. The first three principal gradients were characterized by gradient scores, gradient range, and global dispersion. A three-dimensional gradient space was constructed to assess network geometry, including network eccentricity and inter-network distances. Associations between gradient metrics and drinking behaviors and cognitive performance were also examined. **Results:** Compared with healthy controls, patients with AUD showed no significant global degradation in the first three cortical gradients. However, a trend toward reduced functional differentiation and global dispersion was observed in the second gradient. Significant alterations in gradient scores were detected in multiple cortical regions within the visual, somatomotor, attention, and default mode networks. At the network level, AUD patients exhibited reduced eccentricity in the visual, somatomotor, and ventral attention networks, accompanied by shortened distances between several network pairs (e.g., VIS-VAN, SMN-

VAN, and VAN-FPN), indicating diminished cross-network functional differentiation. The ventral attention network may act as a critical hub mediating perceptual-cognitive hierarchical processing, and its compression may represent a potential neural mechanism of AUD. In addition, the range of the third gradient was negatively correlated with years of alcohol use, suggesting that long-term alcohol exposure may preferentially affect arousal-related cortical dimensions. **Conclusions:** AUD is characterized by preserved global cortical gradient architecture alongside selective disruptions in inter-network functional differentiation, particularly among sensory and attention-related networks. These findings highlight hierarchical reorganization of cortical functional architecture in AUD and provide a systems-level perspective on its neural mechanisms.

Disclosures: S. Lu: None. **Y. Hu:** None. **T. Hong:** None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR326.14/JJ2

Topic: H.08. Drugs of Abuse and Addiction

Support: Ekam Imaging Inc.

Title: Lasting Neurobiological Impacts of Alcohol and THC Combined Use During Adolescence

Authors: *T. MUSKU[1], B. AXE[1], D. ATHREYA[1], T. NELSON[1], S. BALAJI[1], A. MOORE[1], A. BRETTLER[1], S. SHAH[1], A. PHADKE[1], R. J. ORTIZ[2], P. KULKARNI[1], C. F. FERRIS[1]; [1]Northeastern Univ., Boston, MA; [2]Northern Illinois Univ., DeKalb, IL

Abstract: Simultaneous use of alcohol and cannabis during adolescence is rising, yet the long-term neurobiological consequences of this combined exposure remain poorly understood. We explored whether brief, repeated co-exposure to Δ9-tetrahydrocannabinol (THC) and ethanol during a critical developmental window alters brain structure, functional connectivity, and executive behavior in adulthood. Male and female C57BL/6J mice (N = 48; equal sex distribution) were divided evenly into four groups: placebo and weed (PW), alcohol and placebo (AP), polysubstance (AW), and double placebo (PP). Beginning at postnatal day 50, treatments included inhalation of vaporized cannabis (10.3% Δ9-THC), oral gavage of ethanol (31% w/v), exposure to both substances in a 30-minute period, or saline vehicle and THC placebo once daily for ten consecutive days. From postnatal days 110-113, all mice were tested on a battery of behavioral assays probing motor function and working memory. Around postnatal day 117, diffusion-weighted imaging (DWI) and voxel-based morphometry (VBM) were conducted to identify changes in gray-matter microstructure and regional brain volumes. Hypercapnic (CO2) and reward-cue challenges using benzaldehyde during blood-oxygen-level-dependent (BOLD) functional MRI (fMRI), followed by resting-state functional connectivity (rsFC). Co-exposure during adolescence led to the greatest brain microstructure alterations, with reduced apparent

diffusion coefficient values observed in the midbrain and hindbrain, including the ascending reticular activating system responsible for autonomic functions, arousal, and reward pathways. The VBM analysis indicated decreased overall brain volume; alcohol resulted in greater volume reductions in males, while co-exposure led to greater volume reductions in female brains. fMRI results revealed increased BOLD activation in both PW and AW groups, while the AP group showed no significant change. The AW group showed a global increase in rsFC, blunting of connectivity both globally and regionally in the PW group, and mixed changes between brain regions for both AP and PW. Sex-specific differences in exploratory activity and short-term memory were observed during behavioral testing. Overall, alcohol and THC co-exposure during adolescence led to significant changes in brain microstructure, connectivity, and behavior compared to usage of each drug alone. Abnormalities were found in both microstructure and increased connectivity between regions, indicating a long-term change in networks, coupled with sex-dependent shifts in susceptibility to alterations in arousal, reward circuitry, and executive functions.

Disclosures: T. Musku: None. **B. Axe:** None. **D. Athreya:** None. **T. Nelson:** None. **S. Balaji:** None. **A. Moore:** None. **A. Brettler:** None. **S. Shah:** None. **A. Phadke:** None. **R.J. Ortiz:** None. **P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging Inc. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging Inc..

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

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Program #/Poster #: PSTR326.15/JJ3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIAAAA grant R01 AA030368

Title: Altered Reward Processing in Alcohol Use Disorder: An fMRI study

Authors: *B. MEIGHAN[1], H. ATILGAN[2], E. SABA[1], M. BROOKS BURNETT[1], J. R. MATHENA[1], M. E. MCCAUL[1], G. S. WAND[1], A. COTTON[4], J. HUA[3,5], J. E. DESMOND[2]; [2]Neurol., [3]Neurosection, Div. of MRI Research, Dept. of Radiology and Radiological Sci., [1]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Johns Hopkins Univ., Baltimore, MD; [5]F.M. Kirby Res. Ctr. for Functional Brain Imaging, Kennedy Krieger Inst., Baltimore, MD

Abstract: Alcohol use disorder (AUD) has been associated with altered reward processing, and recent studies suggest that the cerebellum may play a bigger role than previously recognized. As part of a larger study investigating cerebellar involvement in AUD, we examined if individuals with AUD differ from controls in neural responses to expected reward outcome (ERO) and reward prediction error (RPE) in a monetary incentive (MI) task. We further explored if lifetime

drinking (LD, quantified in standard drinks via retrospective questionnaire) is associated with activation in *a priori* reward and cerebellar ROIs. We hypothesized that the AUD group would have greater activation in reward areas and the cerebellum for positive RPE, and LD would predict greater ROI activation in positive RPE. Preliminary results are reported for 28 right-handed participants who completed the MI task during fMRI scanning: 11 AUD (2 females), 17 control (5 females) who were screened for Axis I disorders and regular drug use. Controls had no history of AUD or recent heavy drinking/drug use. Neither age nor sex was significantly correlated with LD in either group; hence were not included as covariates. Reward trials were above (positive RPE), below (negative RPE), or equal to expectation (ERO). Contrasts were created for RPE conditions and ERO using SPM12, followed by second-level analyses. The AUD group demonstrated greater BOLD activation in classic reward and cerebellar ROIs than controls during positive RPE. However, they exhibited decreased activation in these regions compared to controls during ERO. Regression analyses indicated that LD is related to ERO — but not positive RPE — activation in a subset of ROIs. In the AUD group, greater LD was positively associated with ERO activation in the right cerebellar lobules VIIIa ($p=.029$) and VIIIb ($p=.04$). Significant group × LD interactions were observed for VTA ($p=.029$) and nucleus accumbens ERO activation ($p=.020$). This manifested as controls having LD that was negatively associated with VTA ERO activation ($p=.043$) and positively associated with left dentate ($p=.038$) and nucleus accumbens ERO activation ($p=.026$). These preliminary findings suggest that AUD may be associated with altered engagement of cerebellar regions alongside classic mesolimbic reward circuitry during reward processing. Additionally, AUD status appears to be a stronger predictor of positive RPE activation than drinking quantity. This potentially suggests that once AUD develops, positive RPE processing is altered, but the magnitude of that alteration is not strongly related to the amount of lifetime drinking.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 5R00AA030806-04

Title: Exploring the role of physical activity in neural projections from the insular cortex to the nucleus accumbens in a genetic risk model for harmful drinking

Authors: *R. ENSTROM, K. GRIGSBY;
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Abstract: Alcohol use disorder (AUD) is characterized by compulsive alcohol consumption and disfunction in interoception—the process of sensing and integrating internal body cues within the insular cortex (IC). Physical activity (PA) improves interoception and is emerging as a powerful adjunctive therapy for AUD; however, the underlying neural circuitry remains largely understudied. We previously found that voluntary wheel running reduced binge-like ethanol drinking in High Drinking in the Dark (HDID-1) mice, a genetic risk model for harmful drinking. Here, we explore whether PA alters ethanol intake by modulating IC projections to the nucleus accumbens (NAc). Adult male and female HDID-1 mice (N = 38; n = 5-8/fluid/PA-group/virus) received AAV2-Cre-GFP in the NAc and an AAV2-DIO-mCherry, -hM3Dq, or –hM4Di in the IC. Following 3 weeks of recovery, mice received intermittent 2h ethanol or water drinking sessions for 3 days, followed by one 4h session the 4th day, for a total of 5 weeks. On the 5th week, running wheels either remained locked (WL) or were unlocked (WR) to allow voluntary PA. Mice underwent repeated measures testing where half the mice received deschloroclozapine (DCZ; 0.1 mg/kg, IP) 3-hours into the dark cycle on days 1-2 and received saline on days 3-4. The other half of the mice received saline on days 1-2 and DCZ on days 3-4. No sex effects were detected; therefore, data were collapsed across sex. A 2-way ANOVA revealed a main effect of DCZ treatment for the Gq-DREADDs groups [$F(1,10) = 3.88$; $p < 0.05$), whereby post-hoc analysis showed reduced ethanol consumption in WR groups, but not wheel-locked groups. Separate 2-way ANOVAs found no main effects for wheel-condition, DCZ treatment, or wheel-condition x treatment interactions for either the mCherry or Gi-DREADD ethanol groups. Similarly, separate 2-way ANOVAs revealed no main effects on water intake for any of the virus groups. These findings demonstrate activating IC → NAc projections decreases ethanol intake in HDID mice engaging in voluntary PA. In contrast, inhibition of this pathway did not alter ethanol intake, indicating the IC → NAc projection may be sufficient (but not necessary) for regulating harmful ethanol drinking. DREADD actuation had no effect on water intake across any virus group, indicating the effects seen were not due to reduction in fluid intake. All virus groups had comparable baseline and VEH ethanol intake, suggesting virus itself does not change fluid intake. Sex is underpowered as a variable in this study, but will be analyzed further as we add more cohorts. Together these findings suggest voluntary PA may enhance the ability of IC → NAc circuitry to suppress binge-like ethanol consumption.

Disclosures: R. Enstrom: None. **K. Grigsby:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 5R01AA028861-04

Title: Inhibiting medial prefrontal cortex following chronic alcohol exposure reduces alcohol seeking and restores cognitive flexibility

Authors: *M. VAHID[1,2], Z. CHANG[2], S. RODRIGUEZ[2], K. YANG[2], S. KROENER[2]; [1]Neurosci., The Univ. of Texas at Dallas, Richardson, TX; [2]Neurosci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX

Abstract: Inhibiting medial prefrontal cortex following chronic alcohol exposure reduces alcohol seeking and restores cognitive flexibility Introduction: Alcohol use disorder (AUD) is a chronic relapsing condition characterized by uncontrollable tendency toward alcohol despite adverse consequences. A key behavioral feature of AUD is impaired cognitive flexibility (CF), the ability to adapt behavior when contingencies change. The medial prefrontal cortex (mPFC) regulates drug seeking and CF. Chronic alcohol exposure may disrupt this role by inducing mPFC hyperexcitability. Thus, we tested whether chemogenetic mPFC inhibition reduces alcohol seeking and restores CF after short- and long-term alcohol exposure. **Method:** Sixty-four C57BL/6 mice were divided into short-term (three weeks) and long-term (two months) exposure cohorts. After initial association learning, mice received bilateral mPFC infusion (0.4 µl) of inhibitory DREADDs or control virus to their mPFC and were assigned to four groups: sucrose-control DREADDs (SD-), sucrose-hM4Di DREADDs (SD+), EtOH-control DREADDs (ED-), EtOH-hM4Di DREADDs (ED+). After alcohol or sucrose self-administration and five days of withdrawal, mPFC neurons were inhibited before cue-induced reinstatement and again before rule-shift (RS) testing. Brains were collected 30 min after RS to confirm viral targeting and assess cFos. In our ongoing TRAP2 experiment, Cre-dependent inhibitory DREADDs are used to tag mPFC neurons activated during reinstatement and selectively inhibit this ensemble during a second reinstatement session and before RS. **Results:** Two-month alcohol exposure significantly impaired CF. Inhibiting the mPFC reduced relapse-related responses during the cue-induced reinstatement session and restored CF to control levels. ED+ mice showed a greater reduction in relapse-related responses with a steep decline in responding within the first 15 min of reinstatement, whereas ED- mice showed a smaller reduction and persistent responding throughout the session. SD- and SD+ mice did not differ, suggesting that mPFC inhibition selectively reduced alcohol-related hyperexcitability rather than general reward seeking. RS performance was impaired in ED- group and restored in ED+ mice, indicating that mPFC inhibition rescued alcohol-induced CF deficits. In short-term cohort, RS performance was not affected and mPFC inhibition did not rescue reinstatement responding. **Conclusion:** These findings suggest that prolonged alcohol exposure promotes relapse-like alcohol seeking and CF deficits through maladaptive mPFC activity, and that inhibiting this activity reduces alcohol-seeking and restores CF.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH 5R01AA028861-04

Title: Chemogenic inhibition of a population of abstinence -activated neurons in the medial prefrontal cortex of alcohol self-administering mice.

Authors: *S. RODRIGUEZ[1], J. T. O'BRIEN[3], K. YANG[4], Z. CHANG[2], M. VAHID[5], S. KROENER[6];
[1]Univ. of Texas Dallas, Plano, TX; [2]Univ. of Texas Dallas, Dallas, TX; [3]Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Univ. of Texas at Dallas, Richardson, TX; [5]The Univ. of Texas at Dallas, Richardson, TX; [6]Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas Sch. of Behavioral and Brain Sci., Richardson, TX

Abstract: Alcohol use disorder (AUD) is associated with prefrontal cortex (PFC) impairments that compromise executive functions, increasing the risk of relapse. In rodents, activation of the prelimbic (PL) and infralimbic (IL) subregions of the PFC is thought to promote alcohol (EtOH) intake and facilitate the extinction of drug-associated memories, respectively. Within these regions, neurons exhibit heterogeneous responses to EtOH. Using a transgenic mouse line (TRAP2/Ai9) that enables fluorescent labeling of neuronal populations active at a defined time point, we identified PL and IL neurons that were active during acute abstinence in mice that self-administered (SA) either alcohol or sucrose across daily operant sessions. Whole-cell patch-clamp current-clamp recordings were performed in PL and IL neurons classified as active (Ai9+) or inactive (Ai9−) following 18-hour of abstinence. Mice in the EtOH group exhibited disproportionately elevated response rates relative to baseline during a cue-induced reinstatement session following five days of abstinence, consistent with the reinforcing properties of EtOH. In the IL, Ai9− neurons showed no difference in firing rates between treatment groups, whereas Ai9+ neurons from EtOH-exposed mice displayed increased spike frequencies, reduced afterhyperpolarization (AHP) amplitude, and decreased action potential (AP) threshold. These indicate differential, substance-specific modulation of excitability within the IL. In the PL, no differences in firing rates were observed between cell populations or treatment groups. These results suggest the existence of a discrete neuronal subpopulation that is active during abstinence and becomes hyperexcitable over an abstinence period and following cue-induced reinstatement. To examine the functional role of these neurons, a separate cohort of animals received intra-IL infusions of either pAAV-hSyn-hM4D(Gi)-mCherry (Addgene) or pAAV-hSyn-mCherry (control virus). Chemogenetic inhibition of Ai9+ IL neurons from EtOH-exposed mice using DCZ during cue-induced reinstatement significantly reduced drug-seeking relative to viral controls, whereas inhibition of Ai9+ IL neurons from sucrose-exposed mice produced no change in reinstatement. These findings indicate that hyperexcitable Ai9+ IL neurons drive cue-induced EtOH-seeking. To identify morphological substrates underlying increased neuronal excitability, we are investigating changes in the axon initial segment (AIS) by comparing AIS length across four cell populations: Ai9+, cFos+, co-labeled Ai9+/cFos+, and NeuN+. We hypothesize that AIS length will be increased in Ai9+ and co-labeled cells.

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Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR326.19/JJ7

Topic: H.08. Drugs of Abuse and Addiction

Title: Behavioral and physiological response to stress and binge-like ethanol drinking in a mouse model of genetic risk for AUD

Authors: *S. PEARSON;
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Abstract: Alcohol use disorder (AUD) is a chronic and relapsing psychiatric disorder with severe physical, mental, and public health consequences. Neuroadaptations induced by excessive ethanol consumption impair critical neural pathways involved in emotional regulation, decision-making, and stress processing, contributing to a reduced ability to respond to stressors and the development of maladaptive behaviors to cope with stress, such as binge-drinking. In humans, AUD has a heritability of nearly 50%. To address the genetic component of AUD, this study used the High-Drinking-in-the-Dark (HDID-1) mouse strain, a powerful model for genetic risk for binge-like drinking which was selectively bred from the low-drinking heterogenous stock Northport (HS/Npt) strain for the propensity to reach high blood ethanol concentrations (BECs) in the Drinking-in-the-Dark (DID) paradigm. Mice (n=5-6/sex/strain/group) underwent multiple 4-day DID sessions to measure binge-like ethanol and water intake prior to (week 1, baseline) and following exposure to the predator odor 2,3,5-trimethyl-3-thiazoline (TMT) in week 2. Physiological stress responses to TMT and ethanol intake were quantified by plasma corticosterone, adrenal gland weights, and expression of stress-related genes (Fkbp4, Fkpb5, Nr3c1, IL-10, IL-6, TNF-α) across brain regions important for reward and stress processing (Nucleus Accumbens, Locus Ceruleus, Central and Basolateral Amygdala, and Bed Nucleus of the Stria Terminalis). Initial results suggest a sex-dependent difference in stress response. A three-way ANOVA revealed a sex by treatment by time effect [$F(1,17)=5.534$; $p = 0.0310$] wherein ethanol intake following TMT exposure was significantly increased in female HDID-1 while significantly decreased in male HDID-1. These findings resemble human studies showing that enhanced ethanol intake following stress is more prevalent among females. These findings further elucidate the complex interplay between traumatic stress and harmful ethanol consumption across both sexes by investigating the behavioral and physiological impacts of stress and binge-like drinking in a unique model which aims to capture the genetic and environmental factors behind AUD development.

Disclosures: S. Pearson: None.

Poster

PSTR326: Circuits, Systems, and Neuroimaging of Alcohol Use

Location: WCC Halls A-C

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Program #/Poster #: PSTR326.20/JJ8

Topic: H.08. Drugs of Abuse and Addiction

Title: Resting-state EEG spectral features of hazardous alcohol use in young adults

Authors: J. L. SCHOLL, L. A. BAUGH, B. M. BYLLESBY, ***T. J. BOSCH**;
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Abstract: Hazardous alcohol use is common during young adulthood and is associated with changes in affective symptoms and intrinsic neural activity. However, brief neural markers that distinguish hazardous from non-hazardous drinking remain underdeveloped. Resting-state EEG provides a scalable measure of intrinsic neural dynamics, and spectral features across canonical frequency bands may capture alcohol-related differences in resting cortical state, arousal, and regulatory control. Here, we tested whether clinical symptoms, resting EEG spectral features, and their combination could classify hazardous drinking status in young adults. Twenty-four participants completed eyes-open and eyes-closed resting-state EEG recordings and self-report measures of alcohol use, depression, and anxiety. Hazardous drinking status was defined from Alcohol Use Disorders Identification Test (AUDIT) scores. Depression and anxiety symptoms were measured using PHQ-8 and GAD-7 scores, respectively. EEG data was cleaned, segmented into 2-s epochs, and used to extract spectral power features across canonical frequency bands. EEG predictors included relative alpha and beta-band power, as well as eyes-open/eyes-closed reactivity measures and band-ratio features. Classification models were trained to distinguish hazardous from non-hazardous drinkers using clinical features alone, EEG features alone, and combined clinical + EEG features. Clinical symptoms alone showed limited classification of hazardous drinking. In contrast, resting EEG features improved classification performance across model comparisons. Hazardous drinkers showed evidence of altered resting-state spectral profiles, including differences in relative alpha power and beta-band reactivity across eyes-open and eyes-closed states. Combined models incorporating both clinical symptoms and EEG features retained strong classification performance, suggesting that resting EEG may capture alcohol-related neural variance not fully explained by concurrent depression or anxiety symptoms. These preliminary findings suggest that hazardous alcohol use in young adults is reflected in altered resting-state spectral organization. More broadly, brief eyes-open/eyes-closed resting EEG may provide a practical approach for identifying candidate neural features associated with alcohol-related risk. Ongoing analyses will test the stability of these spectral predictors, evaluate continuous AUDIT prediction, and determine whether clinical and EEG measures provide complementary information in larger samples.

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Program #/Poster #: PSTR326.21/JJ9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA209403

Title: Social Isolation May Alter Neuronal Excitability of Pyramidal Cells in a Voltage-Dependent Manner in the Prefrontal Cortex of Mice

Authors: *I. GIRGIS[1], V. ZLOTNIK[3,1], A. R. SICHER[4], N. A. CROWLEY[2];
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Abstract: Social Isolation (SI) in humans is associated with negative mental and physical health outcomes across the lifespan including depression and anxiety, cognitive decline associated with dementia, and higher mortality. SI during adolescence interferes with healthy neurodevelopment and is associated with social and emotional problems in adulthood. The prefrontal cortex (PFC) plays a critical role in mediating changes during this time, and its development is highly influenced by social environment and interactions. Disruptions to the PFC, including SI, have been found to prime the brain for future negative neurobehavioral consequences. However, neural mechanisms underlying this impairment are not well understood. Evidence suggests that SI in adolescent mice induces changes in glutamatergic transmission. We hypothesized that social isolation would decrease intrinsic excitability of L 2/3 pyramidal neurons in a sex-specific manner. In this study, we explored how social isolation affects intrinsic excitability in Layer2/3 (L2/3) pyramidal and non-pyramidal (putative GABAergic) neurons in the PFC of mice. Pyramidal neurons are of specific interest because of their role in regulating executive control, cognitive processing, and working memory. The electrophysiological properties of these neurons show how they process signals; providing direct insight into cognitive health in this brain region. Male and female C57BL/6J mice underwent single housing starting at postnatal day 21 (PND21). We used whole-cell patch clamp electrophysiology recordings to investigate the relationship between social isolation and intrinsic excitability of pyramidal and non-pyramidal cells in mice between PND 55-85 with a potassium gluconate-based internal solution at resting membrane potential and -70mV. Preliminary analysis has shown that pyramidal neuron excitability decreased in a voltage dependent manner following social isolation in males but not in females. Ongoing experiments are looking at changes following SI in non-pyramidal neurons in the PFC. These findings could direct future research of SI to consider cell-specific health and firing patterns along with neural sex differences.

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Poster

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Program #/Poster #: PSTR326.22/JJ10

Topic: H.08. Drugs of Abuse and Addiction

Title: Effects of Methylphenidate Modulation of Attention on Neural Responses to Alcohol Cues: Frontostriatal Mechanisms

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Abstract: Individuals with alcohol use disorder (AUD) display heightened activation in reward-related brain regions during fMRI cue reactivity tasks. A major risk factor for AUD is attention-deficit hyperactivity disorder (ADHD), attentional ability has recently been identified as a factor that predicts resilience. We used methylphenidate (MPH) to investigate if enhancing attentional processing can reduce neural reactivity to alcohol cues in individuals with comorbid AUD and ADHD. We hypothesized that MPH administration would be associated with reduced alcohol craving and subcortical activation in response to alcohol cues and strengthen top-down functional connectivity (FC) between regions of cortical attentional control and subcortical reward-related reactivity. Young adults (n = 32, 17 males, ages 18-25) with AUD and ADHD participated in a double-blind, within-subject, placebo-controlled experiment testing a 20mg dose of MPH. Sixty minutes post-pill, participants completed an fMRI task with interleaved blocks of alcohol and neutral beverage images followed by craving ratings. SPM12 was used for preprocessing and first-level analyses. *A priori* regions-of-interest (ROIs) were examined: ventral striatum (VS), dorsal striatum (DS), and amygdala. FC was calculated from VS and pregenual anterior cingulate cortex (pgACC), timeseries extracted in AFNI. Linear mixed models controlling for age and sex in R *lme* revealed a significant main effect of condition, in which alcohol cues elicited greater craving than neutral cues ($\beta = 3.89$, $p < 0.001$). A main effect of treatment revealed lower alcohol craving for MPH versus placebo ($\beta = -12.59$, $p < 0.001$). A significant treatment x ADHD symptom interaction indicated that MPH effects on craving were stronger in individuals with greater ADHD severity ($\beta = 0.43$, $p < 0.001$). ROI models showed a significant treatment x cue interaction ($\beta = -0.14$, $p = 0.024$) in the VS, where MPH reduced the activation in response to alcohol cues relative to neutral cues. Within-subjects mediation analysis of VS-pgACC FC showed MPH attenuates connectivity during neutral images ($\beta = -0.13$, $p = 0.028$), which predicts subsequent suppression of VS activation during subsequent alcohol cues ($\beta = -0.21$, $p = 0.013$). MPH was associated with reduced alcohol craving reports and reduced ventral striatal responses to alcohol cues, suggesting enhanced top-down inhibition, with evidence that ADHD severity may impact efficacy. Pharmacologically enhanced attention may attenuate cue-driven reward processing in AUD, particularly among individuals with ADHD.

Disclosures: J.N. Aloumanis: None. **C. Yu:** None. **S. Nixon:** None. **A. Elton:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.01/JJ11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA009621

Title: Activity of medial prefrontal cortex neurons projecting to the nucleus accumbens core during incubation of methamphetamine craving

Authors: *T. YIU, L. R. TEPE, J. G. WESTLAKE, M. E. WOLF;
Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: A major challenge in treating methamphetamine (meth) use disorder is high risk of relapse even after prolonged abstinence. In the "incubation of craving" model, cue-induced drug seeking in rats progressively intensifies after abstinence from meth self-administration (SA). Previous work from our lab showed that incubation of meth craving is associated with strengthening of excitatory synapses in the nucleus accumbens core (NAcc) by upregulation of calcium-permeable AMPA receptors in medium spiny neurons. However, how upstream glutamatergic inputs to NAcc are recruited during meth incubation remains poorly understood. Here, we used fiber photometry to examine calcium activity in NAcc-projecting prelimbic cortex (PL) neurons during cue-induced meth seeking. Adult male or female rats received viral injections of retrograde Cre in NAcc and Cre-dependent jGCaMP8s in PL, and optical fiber implantation in PL. Rats then underwent meth SA under extended access conditions (6 h/day × 10 days). During SA, nose-pokes in the active hole resulted in meth infusion paired with a light cue; inactive pokes had no consequence. Photometry recordings were performed during cue-induced seeking tests on abstinence day (AD) 1 and AD21, during which pokes in the previously active hole resulted in cue presentation without infusion. In rats from our preliminary cohort that showed sensory-evoked calcium activity during pre-screening, NAcc-projecting PL neurons exhibited a calcium response around pokes in the previously active hole, but not the inactive hole, on AD1 after meth SA. This response appeared to include two components: an initial peak that preceded the active poke, which may reflect active-hole approach or motor initiation, followed by a sustained increase after the poke and cue presentation. Interestingly, a rat that underwent saline SA also showed the pre-poke component around active pokes, consistent with a learned action signal. However, the post-poke response appeared smaller and less sustained than in meth rats. These early results suggest that NAcc-projecting PL neurons are recruited during active seeking behavior, and that this recruitment may be enhanced by meth experience. Studies are underway to determine whether active-poke-related PL-NAcc activity increases from AD1 to AD21 in meth rats while remaining stable in saline controls. In parallel, we are extending this approach to the BLA-NAcc pathway and will also use axon-targeted GCaMP to measure pathway-specific terminal activity in NAcc during meth seeking. Together, these studies will help determine how glutamatergic inputs to NAcc are dynamically recruited during incubation of meth craving.

Disclosures: T. Yiu: None. **L.R. Tepe:** None. **J.G. Westlake:** None. **M.E. Wolf:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.02/JJ12

Topic: H.08. Drugs of Abuse and Addiction

Support: DA009621 to MEW

Title: The role of glutamatergic projections from the paraventricular nucleus of the thalamus to the nucleus accumbens core in incubated methamphetamine craving

Authors: *G. S. DRISCOLL, L. TEPE, H. M. KUHN, L. L. HUERTA SANCHEZ, J. G. WESTLAKE, M. E. WOLF;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: A major barrier to successful methamphetamine (Meth) use disorder treatment is the persistence of vulnerability to craving and relapse. We use the translationally relevant 'incubation of craving' model, in which rats exhibit progressive intensification (incubation) of cue-induced drug craving following withdrawal from drug self-administration, to study the neural mechanisms underlying this vulnerability. We have shown that incubation of Meth craving is associated with upregulation of calcium permeable-AMPARs (CP-AMPARs) in nucleus accumbens core (NAcc) medium spiny neurons (MSN), and that activation of these NAcc CP-AMPARs is required for expression of incubated Meth craving. However, it is important to determine which glutamate inputs to the NAcc contribute to CP-AMPAR plasticity and Meth incubation. One region with robust glutamatergic inputs to the NAcc is the paraventricular nucleus of the thalamus (PVT). We have observed CP-AMPAR upregulation in PVT-NAcc glutamate synapses of Meth-incubated rats and elevated cFos expression in both NAcc and PVT when Meth incubation is expressed, suggesting that the PVT-NAcc pathway contributes to incubated Meth seeking. We therefore used chemogenetics to test the hypothesis that inhibiting the PVT-NAcc terminals will reduce expression of incubated Meth craving. Adult male and female wildtype Long Evans rats received AAV-hM4Di (inhibitory DREADD) into the posterior PVT and bilateral intracranial guide cannulas in the NAcc. Rats learned to self-administer Meth (0.1 mg/kg/infusion, 6 h/d x 10 d), followed by a cue-induced seeking test on abstinence day (AD) 21 preceded by bilateral intracranial infusion of CNO (1 mM in 0.5 µl/side) into the NAcc 30 min prior to the test. Although both sexes are used, our studies are not powered to detect sex differences, as both sexes show meth incubation and NAcc MSN CP-AMPAR upregulation. While no effect was detected with inhibition of PVT-NAcc terminals via intracranial injection of CNO on AD21 (n=12-13/group), a preliminary study (n=3/group) using the same approach but infusing the excitatory DREADD AAV-hM3Dq into the PVT suggested that terminal excitation may reduce expression of incubated Meth craving ($p = 0.0136$ vs. vehicle). Studies are underway to 1) examine the effect of inhibiting NAcc-projecting PVT neurons and their collaterals to other regions by injecting a Cre-dependent inhibitory DREADD into PVT and a retrograde Cre virus into NAcc, and 2) compare the effect of manipulating anterior vs. posterior PVT projections to NAcc. Finally, photometry studies are in progress to measure activation of PVT-NAcc terminals during seeking tests before and after incubation.

Disclosures: G.S. Driscoll: None. **L. Tepe:** None. **H.M. Kuhn:** None. **L.L. Huerta Sanchez:** None. **J.G. Westlake:** None. **M.E. Wolf:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.03/JJ13

Topic: H.08. Drugs of Abuse and Addiction

Support: DA009621 to MEW

Title: CP-AMPAR upregulation in nucleus accumbens synapses during incubation of methamphetamine craving involves retinoic acid signaling and occurs in a cell type- and pathway-specific manner

Authors: *E.-K. HWANG, M. M. BEUTLER, L. R. TEPE, J. G. WESTLAKE, M. E. WOLF; Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: A major problem in treating methamphetamine (meth) use disorder is a high rate of relapse even after prolonged abstinence. In a rat model of drug craving and relapse, cue-induced drug seeking progressively intensifies during abstinence from drug self-administration (SA). Our lab previously demonstrated that abstinence from meth increases synaptic calcium-permeable AMPA receptors (CP-AMPAR) in nucleus accumbens core (NAcc) medium spiny neurons (MSN) and CP-AMPAR activation is required for expression of incubated meth craving. However, the type of MSN (D1 or D2 receptor expressing), the specific glutamate inputs that participate in CP-AMPAR plasticity, and the underlying mechanisms are unknown. Here, we examined cell type- and pathway-specificity of CP-AMPAR upregulation in the NAcc and the contribution of retinoic acid (RA)-mediated homeostatic plasticity, which was recently demonstrated to mediate incubation of cocaine craving. Adult male and female D1- or A2a (the A2aR colocalizes with the D2R)- tdTomato rats self-administered saline or meth under extended-access conditions and received cue-induced seeking tests on abstinence day (AD) 1 and AD21 to establish incubation. Whole-cell patch clamp recordings were performed in early (AD1) and late abstinence (AD21-35) from meth SA. We found upregulation of CP-AMPARs in D1+ but not D1- or A2a+ MSN in the NAcc after withdrawal from meth SA compared to saline controls. Preincubating slices with either a RA synthesis inhibitor or RARα antagonist removed CP-AMPARs from D1+ MSN synapses from meth-incubated rats. Furthermore, combining electrophysiology and optogenetics, we found potentiated glutamatergic synaptic transmission in the medial prefrontal cortex (mPFC) and the paraventricular nucleus of the thalamus (PVT) to NAcc pathways, but not the basolateral amygdala (BLA) to NAcc pathway, after meth incubation. Interestingly, PVT-D1+ MSN synapses showed altered glutamatergic synaptic transmission through upregulation of CP-AMPARs and NMDARs. In contrast, mPFC-D1+ MSN synapses showed increased AMPAR-mediated synaptic responses accompanied by an increased AMPAR/NMDAR ratio without significant changes in CP-AMPAR levels. Our data suggest that abstinence from meth induces CP-AMPAR upregulation through RA signaling in NAcc D1+ MSN and specifically at PVT-D1+ MSN synapses. Despite the complexity of synaptic adaptations depending on the specific inputs, this RA-mediated synaptic adaptation may contribute to the expression of incubated meth craving.

Disclosures: E. Hwang: None. **M.M. Beutler:** None. **L.R. Tepe:** None. **J.G. Westlake:** None. **M.E. Wolf:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.04/JJ14

Topic: H.08. Drugs of Abuse and Addiction

Support: DA009621 to MEW
DA059601 to MEW

Title: Brain regions activated in rats during the expression of incubation of methamphetamine craving

Authors: *L. TEPE, G. S. DRISCOLL, H. M. KUHN, E.-K. HWANG, L. L. HUERTA SANCHEZ, M. E. WOLF;
Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: A challenge in treating methamphetamine use disorder is vulnerability to relapse even after protracted abstinence. To study this, we use the incubation of craving model, in which cue-induced drug craving in rats progressively intensifies (incubates) over the first weeks of abstinence from drug self-administration and then remains high for an extended period. This model has translational relevance because incubation of craving also occurs in persons with substance use disorder, including methamphetamine use disorder, and its plateau phase models the persistence of relapse vulnerability in these individuals. To complement our ongoing studies on the role of the nucleus accumbens and related circuits in the incubation of methamphetamine craving, we are using c-Fos as a marker of neuronal activation to identify brain regions that are activated during the expression of incubated methamphetamine seeking. For all studies, male and female Long-Evans rats self-administer saline or methamphetamine (0.1 mg/kg/infusion; each infusion paired with a light cue) under extended access conditions (6 h/d x 10 d) and receive cue-induced seeking tests on an abstinence day (AD) when incubated seeking has plateaued (AD21-24). During seeking tests, nose-pokes in the previously active port deliver the methamphetamine-paired cue but no drug infusion. Rats are killed 90 min after the start of the seeking test. Immunohistochemistry is performed to detect c-Fos protein. Images are analyzed using Fiji. Significance is set at $p<0.05$. In one cohort of rats (n = 4/group), brains were harvested to compare c-Fos after cue-induced seeking tests in methamphetamine vs saline rats. Meth rats showed greater c-Fos expression than saline rats in the following regions: nucleus accumbens core, paraventricular nucleus of the thalamus (PVT), and basolateral amygdala. In a second cohort (n = 4/group), we compared methamphetamine rats that received a seeking test to identically treated rats that did not undergo a seeking test. So far, the “test group” showed greater c-Fos expression than the “no test” group in the following regions: prefrontal cortex and PVT. Additional rats will be added to both cohorts, and additional regions are being analyzed. A

parallel analysis for incubation of oxycodone seeking is underway. These results can guide future studies of pathways contributing to methamphetamine and oxycodone incubation.

Disclosures: L. Tepe: None. **G.S. Driscoll:** None. **H.M. Kuhn:** None. **E. Hwang:** None. **L.L. Huerta Sanchez:** None. **M.E. Wolf:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.05/JJ15

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA058168

Title: A potential role for nucleus accumbens astrocytes and microglia in incubation of methamphetamine craving

Authors: *J. MCKENZIE, S. E. SWINFORD-JACKSON;
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Abstract: Methamphetamine (meth) use disorder is characterized by cycles of abstinence and relapse. Exposure to meth-related cues during abstinence can contribute to craving, and this increases over time, a phenomenon termed incubation of drug craving. Similar to the time-dependent increase of craving seen in humans, rats trained to self-administer meth and evaluated for meth seeking in early or late abstinence also show an incubation of meth craving. The neural and cellular mechanisms underlying increased meth seeking, and in particular the role of glial cells, remain unclear. Previous studies using cocaine showed alterations to astrocyte morphology and expression of several receptors were associated with altered cocaine seeking behavior. Likewise, microglia have been shown to impact cocaine seeking behavior through varying mechanisms. We hypothesize that astrocytes and microglia in the nucleus accumbens will be altered during late vs. early abstinence from meth, corresponding with the incubation of meth craving. Male and female rats received surgery to implant a catheter into the jugular vein. After recovery, rats underwent 14 days of meth self-administration during which responding on the active lever on a fixed ratio 1-5 schedule resulted in an intravenous dose of meth (0.1 mg/kg/infusion) paired with a light cue. Rats were evaluated for meth seeking behavior and perfused for fluorescent immunohistochemistry on forced abstinence day 1 or day 30. Sections of the nucleus accumbens will be stained for GFAP and Iba1 to visualize astrocytes and microglia. Astrocytes and microglia will be scored by surface area, process length, and complexity to analyze morphological changes. Additionally, expression of astrocyte and microglia receptors and markers that have previously been shown to impact cocaine seeking behavior will be quantified. We replicated previous findings that active lever responding for previously-paired meth cues, our operational definition of meth seeking, was higher on abstinence day 30 than abstinence day 1. Studies to examine astrocyte and microglia morphology at early vs. late

abstinence are ongoing. Completion of these studies will suggest a role for nucleus accumbens astrocytes and microglia in the incubation of meth craving, which will be functionally interrogated in future studies.

Disclosures: J. McKenzie: None. **S.E. Swinford-Jackson:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

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Program #/Poster #: PSTR327.06/JJ16

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA062680
NIH Grant R01DA038058
NIH Grant R01DA056484

Title: Novel Platform For Modeling Amphetamine Escalation in Drosophila

Authors: *C. ROWE, A. GALLI;
Surgery, Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Amphetamine (AMPH) Use Disorder (AUD) affects millions worldwide, driving compulsive drug-seeking and escalating intake that persist despite severe health, social, and economic consequences. To study the etiology of AUD, addiction scientists developed mammalian behavioral models focusing on compulsive drug-seeking, escalation of drug intake, heightened motivation of drug consumption, as well as persistence of drug intake despite adverse consequences. These models rely on the use of expensive, complex, and ethically challenging mammalian models. To begin to address these barriers and enable large-scale genetic and pharmacological studies, we developed the Fly Liquid-food Interaction Escalation Assay (FLIEA) to model escalation of drug intake using Drosophila melanogaster. Refining the Fly Liquid-food Electroshock Assay (FLEA) for greater signal reliability and multi-day behavioral tracking, FLIEA quantifies how flies interact with sucrose solutions with or without AMPH to capture the progressive changes that define escalation of drug intake. In Canton-S flies, AMPH-laced sucrose elicited a robust escalating-like phenotype: with repeated exposure, flies interacted with the drug-containing solution more overall, more aggressively, and more frequently than with sucrose alone. This emerged across six complementary metrics spanning total interaction amount, interaction frequency, maximum effort per session and per feeding bout, continued pursuit of the drug once engaged, and latency to maximum effort once engaged. Critically, these metrics correlate to key components of AUD including escalation of AMPH intake, which supports the notion that conserved molecular mechanisms across species drive AUD-associated phenotypes without reliance on mammalian neural circuitry. Thus, Drosophila represents a highly tractable genetic model for dissecting AUD's molecular mechanisms with high translational validity. FLIEA's cost-effectiveness and scalability could facilitate rapid genetic

screening and stratifying experimental groups into subpopulations based on high and low escalating individuals to accelerate the discovery of novel therapeutic targets for the treatment of AUD.

Disclosures: C. Rowe: None. **A. Galli:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH 1R01DA056484
NIH 1R21DA059844
UAB Microbiome Center Core Services Award
UAB CNC Pilot Award

Title: Bugs and drugs: Fusobacterium nucleatum Biofilms as key regulators of Amphetamine abuse.

Authors: *C. GONZÁLEZ-ARANCIBIA[1], S. NAKKELLA[1], Y. ZHU[1], A. SUNIL KUMAR[1], H. TRAN[1], S. PHIPPS[1], J. T. HOCHSTETLER[2], N. DANG[1], C. ROWE[1], C. E. HERNANDEZ[1], S. J. MABRY[3], A. GALLI[1], A. M. CARTER[1];
[1]Surgery, [2]Microbiology, Univ. of Alabama at Birmingham, Birmingham, AL; [3]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Changes in the composition of the gut microbiome, also known as dysbiosis, are associated with a range of pathologies, including neurological disorders. Consistently, antibiotic administration can affect multiple aspects of behavior, including behaviors governed by the dopaminergic system. Antibiotics reduce amphetamine (AMPH)-induced behaviors and extracellular dopamine (DA) levels in rodents, suggesting that microbes could play a role in modulating host responses to psychostimulants. Previous data from our lab showed that *Fusobacterium nucleatum* (*F. nucleatum*) colonization of fruit flies (*Drosophila melanogaster*) enhances AMPH-associated behaviors such as locomotion and courting. Consistent with these behaviors being regulated by DA signaling, we also found that *F. nucleatum* increases expression of the dopamine transporter (DAT) and, thereby, enhances AMPH-induced DA efflux in the brains of flies. AMPH abuse also alters the microbial composition of the gut, increasing the abundance of fusobacteria in both rodents and humans. *F. nucleatum* is an anaerobic bacterium found primarily in the oral cavity of humans. How AMPH enhances *F. nucleatum* abundance is unknown. We found that AMPH increased biofilm formation in *F. nucleatum* cultures. *F. nucleatum* forms biofilms to establish an oxygen-free niche to facilitate colonization of oxygenated environments. RNA sequencing and qRT-PCR revealed that AMPH upregulates *fap2, radD*, and *fadA* gene expression in *F. nucleatum*. These genes encode adhesion proteins

that facilitate the attachment of *F. nucleatum* to surrounding surfaces and other bacteria. We also found that mutant bacteria lacking the *fap2* gene (Δfap2) do not form biofilms, even in the presence of AMPH, and that fap2 and biofilm formation are required for AMPH-enhancement of *F. nucleatum* colonization of flies. Additionally, flies administered Δfap2 *F. nucleatum* exhibited lower AMPH-induced DA efflux and less AMPH intake than that observed in flies colonized with wildtype *F. nucleatum*. These data suggest that biofilm formation is required for AMPH enhancement of host colonization by *F. nucleatum* and for supporting AMPH-induced dopaminergic signaling. We propose a biofilm-dependent feed-forward paradigm for AMPH-associated behaviors: AMPH increases the abundance of *F. nucleatum* by upregulating biofilm formation, and *F. nucleatum* enhances responses to AMPH by increasing DAT expression and AMPH-induced DA efflux.

Disclosures: C. González-Arancibia: None. **S. Nakkella:** None. **Y. Zhu:** None. **A. Sunil Kumar:** None. **H. Tran:** None. **S. Phipps:** None. **J.T. Hochstetler:** None. **N. Dang:** None. **C. Rowe:** None. **C.E. Hernandez:** None. **S.J. Mabry:** None. **A. Galli:** None. **A.M. Carter:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.08/JJ18

Topic: H.08. Drugs of Abuse and Addiction

Support: MSU Psychology
MSU COSE

Title: Changes in bout organization that suppress activity during acute psychostimulant withdrawal

Authors: *W. WHITE[1], I. M. WHITE[2];
[2]Psychology, [1]Morehead State Univ., Morehead, KY

Abstract: Typically, rats are active in bouts or episodes that occur approximately every two hours and that are about 20 minutes in duration. Our previous report indicated that amphetamine (2 mg/kg) and morphine (5 mg/kg) altered bout organization similarly 13-24 hours after administration, producing reduced activity, a sign of acute withdrawal. This study compared two psychostimulants, methamphetamine and amphetamine, for their ability to alter bout organization and reduce activity indicative of acute withdrawal. The activity of male rats was monitored in open fields having bedding, food, water, and a 12/12 hour light/dark cycle. Rats were treated with saline, methamphetamine (1.5 mg/kg), or amphetamine (2 mg/kg), and their activity was monitored for 24 hours. Treatments occurred near light onset. The number of bouts, the time between bouts, the duration of bouts, and the amplitude of bouts were quantified. Amphetamine reliably reduced activity 13-24 hours post-treatment by producing rather small changes in all bout parameters, while the basic episodic organization of activity remained intact.

Methamphetamine showed a similar pattern. Though their pharmacological action on synaptic transmission may differ, both drugs appeared to modify bout organization similarly. Our findings suggest that both drugs may produce a sign of acute withdrawal via a common mechanism and that the mechanisms involved in the basic organization of episodic activity and acute withdrawal may differ.

Disclosures: W. White: None. **I.M. White:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.09/JJ19

Topic: H.08. Drugs of Abuse and Addiction

Title: Systematic review of methamphetamine use during pregnancy.

Authors: *C. A. CASTAÑEDA NAVARRETE;
Univ. of Guadalajara, Guadalajara, Mexico

Abstract: Systematic review of Methamphetamine uses during pregnancy.
Introduction
The increase in methamphetamine (crystal meth) use among pregnant women worldwide is alarming due to its effects on the fetus. These consequences can include lower gestational age, lower birth weight, smaller head circumference, shorter neonatal body length, structural brain abnormalities, impaired cognitive and motor development, impaired inhibitory control, attention deficits, neurodevelopmental problems, and behavioral problems.
The objective of this systematic review is to identify the different consequences of methamphetamine use during pregnancy on the child, as well as to formulate consequence algorithms based on previous research on the effects of prenatal methamphetamine exposure.
This systematic review examines the developmental outcomes of children prenatally exposed to methamphetamine using PubMed, systematically searching for studies up to 2026.The findings indicate different approaches for analyzing outcomes,identifying various characteristics to formulate care pathways for children exposed to methamphetamine during gestation, such as sequelae like neonatal abstinence syndrome, newborn characteristics (Apgar score), and the sociodemographic characteristics of the country, in this case, Mexico.
Conclusions
Further studies should be conducted to formulate care pathways for children exposed to methamphetamine, as well as to create algorithms for their care and formulate an evidence-based stimulation plan for the child.
Keywords
Prenatal exposure, methamphetamine, birth outcomes, Neurodevelopment

Disclosures: C.A. Castañeda Navarrete: None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

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Program #/Poster #: PSTR327.10/JJ20

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH P30DA048472, Center for Neural Circuits in Addiction
UMN Medical Discovery Team on Addiction

Title: Changes in BOLD activity elicited by drug-paired cues in rodent addiction models

Authors: *R. L. YOUNK[1], J. ZIMMERMANN[2], M. J. THOMAS[3];
[1]Univ. of Minnesota, Twin Cities, Minneapolis, MN; [2]Dept. of Neurosci., [3]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Drug-associated cues can drive relapse in substance use disorder (SUD). Cue-induced memories initiate craving by activating sensory and reward-related brain regions. Human functional magnetic resonance imaging (fMRI) studies reveal functional circuits linked to drug vs. non-drug associated cues, regardless of the primary drug of use. In parallel rodent studies, drug vs. non-drug cues activate distinct yet overlapping functionally connected neuronal populations (meta-ensembles). While cue-responsive regions and meta-ensembles have been generalizable across drugs of abuse, these studies primarily investigated responses to nicotine, alcohol, and cocaine- associated cues. It is still unknown how cue-responsive activity changes in response to other drugs of abuse. Our study aims to address this in rats by identifying regions responsive to methamphetamine (meth) associated cues and their functionally connected meta-ensembles.

We combined fMRI and a conditioned place preference (CPP) paradigm to assess brain-wide responses to meth associated cues. In CPP, two distinct odors were paired with saline or meth (n=2 rats) twice daily over twelve days. Conditioning was assessed in 20-minute preference sessions by time spent with the CS+ (meth) minus CS- (saline) odor. CPP produced a preference for the CS+ in both animals (mean preference = +166s). Rats were anesthetized and their brains functionally imaged for odor-responsivity in a 9.4T scanner pre and post the CPP paradigm. 10-minute functional scans included 7 10-second exposures per odor with ~30-second inter-trial-intervals. To assess functional changes in response to the CS+ and CS- odors, we calculated percent change in blood oxygen level dependent (BOLD) activity throughout the brain. Within atlas-defined regions, percent change BOLD was calculated over each odor presentation and 15 seconds post using a pre-odor baseline. Post CPP, rats showed increases in % change BOLD to their CS+ odor compared to their CS- odor in multiple areas associated with sensory processing and reward.

These preliminary results corroborate current clinical and preclinical literature on other drugs of abuse. Further network analyses could elucidate functional relationships between these brain regions. We expect to find distinct patterns of activity in response to meth vs saline-paired odors across cortical and subcortical structures, indicating a drug-related reward-processing network.

These meta-ensembles may provide further evidence of a generalizable drug-cue responsive functional network with central regions serving as basis for targeted investigation and SUD treatments.

Disclosures: R.L. Younk: None. **J. Zimmermann:** None. **M.J. Thomas:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

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Program #/Poster #: PSTR327.11/Web Only

Topic: H.08. Drugs of Abuse and Addiction

Title: Hippocampal D2-like dopamine as a novel target for the effect of Cannabidiol on modulating extinction and reinstatement of methamphetamine-seeking behavior

Authors: *R. AZIZBEIGI[1], S. E. OMIDIANI[2], A. HAGHPARAST[2];
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Abstract: Methamphetamine (METH) is a serious health concern with no reliable pharmaceutical treatment. It may disrupt the reward system and dopaminergic transmission. METH's rewarding qualities are associated with a rise in dopamine. Additionally, Cannabidiol (CBD) is a non-psychoactive substance derived from marijuana. It is well established that CBD attenuates the reinforcing effects of drugs of abuse, significantly affects dopaminergic transmission and may aid in reward-and addiction-related behaviors. Multiple lines of evidence suggest that CBD exert its effects by modulating the mesocorticolimbic dopamine system. D2-like receptors in the CA1 region of the hippocampus plays a significant role in relaying memory and emotional signals related to the mediating the effects of CBD on METH-seeking behavior during extinction and reinstatement In the conditioned place preference (CPP) model. For this purpose, rats were administered various doses of Sulpiride (0.25,1, or 4 μg/0.5 μl) as a D2-like receptor antagonist before intracerebroventricular (ICV) injection of CBD (10 μg/5 μl) during a 10-day extinction period. Additionally, a separate group of rats received Sulpiride (0.25,1, or 4 μg/0.5 μl) before a single CBD injection (50 μg/5 μl) on the reinstatement day. The findings indicated that Sulpiride (1 and 4 μg) significantly attenuated CBD's acceleration of METH-CPP extinction ($p < 0.01$ and $p < 0.05$, respectively). Moreover, Sulpiride (1 and 4 μg) during the reinstatement phase notably reversed CBD's preventive effects on the reinstatement of reward-seeking behavior ($p < 0.05$ and $p < 0.001$, respectively).According to the current research, CBD dramatically reduced the extinction period and suppress METH reinstatement is partially mediated through interaction with D2- like dopamine receptors in the CA1 region of the hippocampus. These finding proposed that new insight into more precise and effective intervention for METH use disorder.

Disclosures: R. Azizbeigi: None. **S.E. Omidiani:** None. **A. Haghparast:** None.

Poster

PSTR327: Mechanisms of Amphetamine Use and Addiction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR327.12/JJ21

Topic: H.08. Drugs of Abuse and Addiction

Support: This work is supported by NIDA-IRP

Title: Incubation of methamphetamine craving after food choice-induced voluntary abstinence is not associated with VTA circuit activation

Authors: R. PATIL[1], G. D'OTTAVIO[2], K. NEGISHI[3], A. SULLIVAN[6], J. M. BOSSERT[7], Y. SHAHAM[4], ***H.-L. WANG**[5];
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Abstract: BACKGROUND: We and the Caprioli lab reported time-dependent increases (incubation) in methamphetamine (Meth) seeking after food choice-induced abstinence. This effect depends on dopamine receptors in nucleus accumbens (NAc), a target of ventral tegmental area (VTA) dopamine projections. Here, we investigated whether incubation is associated with: (1) activation (measured by Fos) of dopaminergic and non-dopaminergic VTA neurons, and (2) recruitment of VTA-projecting afferent inputs. We used double labeling of Fos and tyrosine hydroxylase (TH) in VTA, combined with retrograde tracing (fluorogold [FG] injections into VTA) and Fos labeling in projection regions. METHODS: We trained rats (n=28) to self-administer food pellets (6 days, 6 h/day), followed by Meth (12 days, 6 h/day). We assessed Meth seeking on abstinence day 1 or after food choice-induced abstinence on day 15. We collected brains from Test groups 90 min after testing and from No-test groups one day later. We quantified Fos+TH labeling in VTA and FG+Fos double-labeling in projection regions. RESULTS: Meth seeking increased after 15 abstinence days versus 1 day (incubation). VTA Fos expression occurred primarily in interfascicular nucleus and in both TH-positive and TH-negative neurons. Fos counts were higher in rats tested on day 1 or 15 than in no-test controls. Incubation was not associated with increased Fos expression in either neuronal population. Incubation was also not associated with Fos+FG double-labeling in VTA projection regions, including NAc, medial prefrontal cortex, and preoptic nucleus. CONCLUSION: Results suggest that incubation of Meth craving after food choice-induced abstinence is not driven by enhanced activation of VTA neurons or VTA afferents.

Disclosures: R. Patil: None. **G. D'Ottavio:** None. **K. Negishi:** None. **A. Sullivan:** None. **J.M. Bossert:** None. **Y. Shaham:** None. **H. Wang:** None.

Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.01/JJ22

Topic: H.08. Drugs of Abuse and Addiction

Support: The University of Michigan NIDA Training Program in Neuroscience: T32 DA007281
Rackham Merit Fellowship (University of Michigan)
NIH Grant DA065668

Title: An integrated view of the effects of nicotine on mesolimbic dopamine neurons

Authors: *J. SEDDON[1], P. F. KRAMER[2];
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Abstract: Nicotine use disorder (NUD) is one of the most common substance use disorders and remains a leading cause of preventable death in the United States. NUD results from chronic nicotine exposure, producing persistent neuroadaptations in the brain's reward circuitry that reinforce compulsive drug seeking and make cessation difficult. It is well understood that nicotine acts on nicotinic acetylcholine receptors (nAChRs) on dopaminergic neurons to drive compulsive drug seeking. However, current methods lack the resolution to determine how nicotine modulates dopaminergic axon physiology and morphology. Consequently, a critical mechanistic gap persists in our understanding of NUD. By performing patch-clamp recordings from dopaminergic soma, medial forebrain bundle axons, and nucleus accumbens terminals, we examined how acute nicotine exposure alters membrane properties, firing frequency, and other features of propagating action potentials recorded in the axon of dopaminergic neurons. These experiments will determine how nicotine changes the excitability and function of distinct compartments of the neuron to develop a complete view of the impact of nicotine on dopamine neurons. Moreover, we examined the physical structure of dopaminergic axons in the NAc core to quantify their arborizations are in this reward-related region. At present, we have observed that there is heavy cholinergic modulation in the NAc core. In the presence of nicotine, cholinergic inputs to the NAc terminals are reduced, but not eliminated. In the medial forebrain tract of axons there is, by contrast, a consistent depolarization of the resting membrane potential in the presence of nicotine. These findings collectively suggest that acute exposure to nicotine interacts with propagating action potentials in the NAc terminals where dopamine is released depending on the intrinsic activity on the dopaminergic axon.

Disclosures: J. Seddon: None. **P.F. Kramer:** None.

Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.02/JJ23

Topic: H.08. Drugs of Abuse and Addiction

Title: Chronic stress enhances while environmental enrichment attenuates nicotine-seeking behavior in animal models of addiction

Authors: D. ANDERSON, M. MCMICHAEL, A. SYMICEK, ***J. J. CORTRIGHT**;
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Abstract: Research indicates that individuals exposed to stress are more vulnerable to drug addiction (Koob, 2008; Ouimette et al., 2007). For example, acute stress exposure increases and reinstates nicotine-seeking behavior as measured by conditioned place preference (CPP) (Leão et al., 2009) and chronic unpredictable stress increases the response to nicotine-rewarding properties in the CPP test (Biala et al., 2018). Contrary to the effects observed following exposure to variable stress, both running and environmental enrichment (EE) reduce CPP for cocaine (Mustroph et al., 2016). Based on the interactions observed between EE and chronic stress on learning and memory (Wright & Conrad, 2008), it is reasonable to postulate similar interactions on the rewarding properties of nicotine. Thus, these experiments assess the ability of repeated exposure to variable stress to augment nicotine-seeking behavior and relapse in animal models of drug addiction and determine whether EE can reverse, or abolish, the enhancement in the rewarding properties of nicotine following exposure to chronic variable stress. Long-Evans rats were exposed to either 20 days of randomized stressors, four weeks of EE, or 20 days of randomized stressors followed by four weeks of EE. Control animals did not receive any exposure treatment. Following exposure treatment animals underwent CPP to nicotine (0.175 mg/kg, base, s.c.) or allowed to self-administer nicotine (0.03 mg/kg/infusion) under fixed ratio schedules of reinforcement. Responding under a progressive ratio schedule of reinforcement was also assessed, a measure that reflects the motivation to self-administer nicotine. Following up to 20 days of extinction training, rats were tested for nicotine-seeking behavior reinstatement by a non-contingent injection of nicotine (0.4 mg/kg, IP). Rats exposed to chronic stress acquired nicotine self-administration at a faster rate relative to controls, exhibited enhanced motivation to obtain the drug, were more resistant to nicotine extinction, and showed enhancements in nicotine-primed reinstatement. Data also indicate that animals exposed to chronic variable stress exhibit higher place preference for nicotine compared to controls, an effect that is attenuated by exposure to EE. Therefore, in addition to providing evidence that chronic stress can enhance the motivational effects of nicotine and the contributions of stress and environmental conditions to successful cessation of drug-seeking, the results obtained can have important implications for the use of environmental stimulation together with pharmacological and behavioral therapies in the treatment of addiction.

Disclosures: D. Anderson: None. **M. McMichael:** None. **A. Symicek:** None. **J.J. Cortright:** None.

Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.03/JJ24

Topic: H.08. Drugs of Abuse and Addiction

Title: Effects of parental preconception stress on nicotine-seeking behavior in offspring

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Abstract: Substance use remains highly prevalent with products like vapes and e-cigarettes becoming one of the most widely accepted forms of substance use. Nicotine remains very relevant, as tobacco and other vaping products are continually being consumed worldwide, and exposure to tobacco products can alter behavior and neurobiology from generation to generation (Goldberg et al., 2021). Exposure to chronic stress has been found to impact human development and the development of disease, resulting in an increased risk of exhibiting substance seeking behavior (Jenkins et al., 2021). The effects of parental exposure to stimuli on subsequent developmental changes has previously been studied using models of fear conditioning in rats whose parents were exposed to odorous or shocking stimuli. Such studies utilized conditioned fear responses to acetophenone, which activates an odorant receptor (Olfr151), in paternal rats prior to conception to analyze transgenerational and multigenerational effects on following generations. Altered epigenetic marks, specifically DNA hypomethylation in sperm of F0 and F1 generations, were found to attribute to transgenerational inheritance of behavioral and neurotomical changes in offspring without prior exposure to the odor (Dias & Ressler, 2014). Few studies, however, have investigated the epigenetic effects on enhanced nicotine seeking behavior of offspring of adult rats exposed to chronic variable stress. Therefore, this study will investigate the effects of prenatal preconception chronic variable stress on conditioned place preference to nicotine in subsequent generations and the epigenetic processes involved. One group of Long-Evans rats were exposed to 20 days of randomized stressors, while control rats did not receive any exposure treatment. Following exposure treatment animals were bred and offspring underwent place preference conditioning to nicotine (0.175 mg/kg, base, s.c.). To date, data indicate that animals bred from a mother exposed to chronic variable stress exhibit higher place preference for nicotine compared to animals bred from controls. In addition to providing evidence of how the experiences of a parent before conceiving offspring can influence the function of the nervous system and behavior of offspring, the results obtained can have important implications for the treatment of addiction.

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Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.04/KK1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA Grant UG3DA048510

Title: Anxiety and Nicotine Dependence: The Effects of Anxiety on rIFG TBS Outcomes Among Nicotine Dependent Individuals

Authors: *S. J. PRIDE[1], N. J. HENIGMAN[2], S. UPTON[3], B. FROELIGER[4];
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Abstract: Tobacco use disorder (henceforth nicotine addiction) continues to be the leading cause of preventable premature death and disease in the U.S. Individuals diagnosed with anxiety, defined as having excessive worry and apprehensive expectations, smoke at a disproportionately higher rate, have greater nicotine dependence severity, and lower cessation success as compared to the general population. Mechanistic research has suggested that disrupted prefrontal-mediated executive function (e.g., Inhibitory control [IC] and proactive regulation of craving [ROC]) contributes to the ongoing maintenance of nicotine use; however, the effects of anxiety on prefrontal-mediated executive function in the context of nicotine dependence have not been well characterized. Theta Burst Stimulation (TBS) is a pattern-specific type of rTMS that has shown effectiveness in reducing depressive and anxiety symptoms, and it's being researched and developed for other disorders, such as Tobacco Use Disorder (TUD). Specifically, Continuous Theta Burst Stimulation (cTBS) of the right inferior frontal gyrus (rIFG) has been shown to improve IC and reduce smoking behavior. This randomized study recruited 37 nicotine-dependent adults. Participants underwent functional magnetic resonance imagining (fMRI) scans before and after receiving two forms of TBS in a randomized order on two separate study visits: cTBS and iTBS. Data were analyzed using mixed-design repeated-measures ANOVA to examine the effects of anxiety symptom severity group (between-subject) and stimulation condition (within-subject) on smoking outcomes. No significant BAI Group by Stimulation condition interaction was found for IC task performance. Consistent with prior findings, a significant main effect for stimulation condition showed that cTBS improved IC task performance relative to iTBS. For smoking behavior, there was a significant main effect of BAI Group by Stimulation condition, demonstrating that the effects of TBS differed by anxiety level ($p = .042$). Furthermore, simple effects revealed that individuals with high anxiety symptom severity experienced a significantly greater decrease in smoking after receiving cTBS compared to iTBS ($p = .034$). These preliminary findings demonstrate that cTBS improves IC independent of anxiety symptom severity; however, is most effective for reducing smoking behavior among individuals with higher levels of anxiety. These findings provide a potential pathway to improve smoking outcomes in a high-risk group of individuals who smoke with comorbid anxiety.

Disclosures: S.J. Pride: None. **N.J. Henigman:** None. **S. Upton:** None. **B. Froeliger:** None.

Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.05/KK2

Topic: H.08. Drugs of Abuse and Addiction

Title: Neurobehavioral mechanisms associated with vaping cessation in adolescents: implications for addiction prevention and mental health. Systematic Review

Authors: *J. ARIAS-RICO[1], E. RAMÍREZ MORENO[2], R. BALTAZAR TELLEZ[6], J. AGUILAR GUTIÉRREZ[3], D. MOLINA AVILEZ[4], L. RIVERA-RAMIREZ[4], C. DIMAS RESENDIZ[5], O. MARTÍNEZ[7];
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Abstract: The use of electronic cigarettes or vaping devices has become a significant public health problem among adolescents. Various studies have demonstrated that early exposure to nicotine can affect neurocognitive processes related to decision-making, inhibitory control, emotional regulation, and brain reward circuits. Although a considerable proportion of adolescents express a desire to quit vaping, nicotine dependence, peer influence, inadequate stress management, and low risk perception represent significant barriers to achieving this. Recent studies suggest that neurobehavioral factors such as self-efficacy, emotional regulation, harm perception, and motivation for change play a fundamental role in vaping cessation. The aim is to analyze the available scientific evidence on the neurobehavioral mechanisms associated with vaping cessation in adolescents, identifying the main factors that facilitate or hinder the cessation of electronic cigarette use. A systematic review of the scientific literature published in biomedical and health sciences databases was conducted. Observational studies, and qualitative studies focused on adolescent e-cigarette users were selected. Variables related to intention to quit, cessation attempts, nicotine dependence, risk perception, self-efficacy, emotional regulation, social influence, and coping strategies were analyzed. The evidence indicates that the perceived risk associated with vaping is one of the most important predictors of intention to quit. Likewise, self-efficacy, intrinsic motivation, emotional regulation skills, and family support are associated with a greater likelihood of successful cessation. Conversely, nicotine dependence, the simultaneous use of other tobacco products, peer influence, and vaping as a strategy to manage anxiety or stress decrease the likelihood of quitting. Recent studies report that over 70% of adolescent vaping users express an intention to quit, and approximately two-thirds have made at least one attempt to do so. However, barriers such as addiction, fear of failure, poor emotional control, and social pressure continue to limit therapeutic success. The neurobehavioral mechanisms associated with vaping cessation in adolescents involve the interaction of cognitive, emotional, and social factors. Self-efficacy, harm perception, emotional regulation, and social

support are protective elements that promote cessation. The development of preventive programs and neuroscience-based interventions aimed at strengthening these mechanisms could increase cessation rates and reduce the neurobiological consequences of early nicotine exposure.

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Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.06/KK3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant P20GM109097
NIH Grant K23DA042898

Title: Childhood Emotional Maltreatment Predicts Nicotine Dependence and Resting-State Self-Control Connectivity in Adults who Smoke Daily

Authors: *A. C. DREW[1], J. AVERY[2], F. J. MCCLERNON[5], B. LAMICHHANE[3], W. K. SIMMONS[4], A. BALTAZAR[6], T. LOVE[8], J. A. OLIVER[7];
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Abstract: Adverse Childhood Experiences (ACEs) have emerged as important risk factors for substance use and nicotine dependence, yet neurobiological mechanisms linking early emotional maltreatment to nicotine dependence remain unclear. Emerging evidence further suggests that ACEs are associated with alterations in wide-scale differences in brain connectivity in cortical networks implicated in cognitive and emotional regulation. We examined whether a factor indexing childhood emotional maltreatment predicted nicotine dependence severity and brain connectivity measures in adult daily smokers.Adults who smoked daily (N=46) completed two counterbalanced fMRI sessions — one following 24-hour abstinence, one following ad lib smoking — plus baseline assessments including the Maltreatment and Abuse Chronology of Exposure (MACE) and Fagerström Test for Nicotine Dependence (FTND). A four-subscale emotional maltreatment (EM) factor (emotional neglect, non-verbal emotional abuse, parental verbal abuse, peer emotional abuse) was derived from the MACE via factor analysis in an independent community sample (n=261; 61% variance explained) and projected onto study participants. rIFG-preSMA connectivity, a circuit involved in response inhibition (Schaum et al., 2021) and the Resource Allocation Index (RAI), an index of large-scale network coupling (Lerman et al., 2014), were examined using linear mixed-effects models covarying session and

head motion. The EM factor predicted nicotine dependence severity (r=+.43, p=.006). Higher EM was associated with weaker rIFG-preSMA connectivity in the sated state (r=−.42, p=.014), but there was no effect of session on rIFG-preSMA connectivity (p=0.17). RAI was significantly different between nicotine abstinent and sated sessions (β=−0.23, p=.002), replicating previous results, but this difference was not related to EM (β=+0.02, p=.68). Childhood EM predicts nicotine dependence and reduced connectivity in a self-control circuit under sated conditions. Its dissociation from RAI, a state-sensitive index of large-scale network allocation, suggests a stable trait marker of self-regulatory circuitry rather than a withdrawal-related state effect, implicating disrupted inhibitory control circuitry as a neurobiological pathway linking early adversity to enduring nicotine dependence.

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Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.07/KK4

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA047413
Baylor University Undergraduate Research and Scholarly Achievement Grant

Title: Acute and lasting neurobehavioral effects of adolescent nicotine and "dry hit" vapor exposure in male Wistar rats

Authors: *A. G. OGDEN[1,2], S. WRIGHT[1], S. V. KASARAM[1], S. MOUTOS[1], C. L. WERNETTE[1], M. I. H. DEJEUX[1], K. E. ROJAS[1], C. M. SAYES[2], J. D. NGUYEN[1]; [1]Dept. of Psychology and Neurosci., [2]Sch. of Earth and Envrn. Sci., Baylor Univ., Waco, TX

Abstract: E-cigarette use amongst adolescents and young adults remains high. An additional risk unique to e-cigarettes is “dry hitting,” a phenomenon where the e-liquid level in a refillable cartridge gets low enough to cause the coil to burn. Dry hit vapor has been shown to produce toxic chemical byproducts including acetaldehyde, ketene, formaldehyde, acrolein, and acetone. Furthermore, perineuronal nets (PNNs) are specialized extracellular matrix structures known for their role in synaptic stabilization. We hypothesized that subjects exposed to repeated nicotine vapor inhalation and dry hits would have differential behavioral responses and expression of PNNs in the amygdala and insular cortex. Subjects were exposed to 30 minutes of vapor inhalation at varying doses for seven consecutive days during adolescence. Locomotor activity assessment, thermal antinociception (i.e. tail withdrawal test), elevated plus maze were used to confirm acute drug intoxication, sensitization, and tolerance. A subset of the subjects were aged to post-natal day 80, exposed to nicotine vapor, and performed the locomotor activity assessment. Immunohistochemistry was used to identify perineuronal nets in the regions of

interest. Nicotine vapor inhalation dose-dependently decreased spontaneous locomotor activity given acutely and produced locomotor sensitization given repeatedly; “dry hits” significantly potentiated the effects of nicotine. Repeated inhalation of nicotine vapor induced antinociceptive tolerance as measured by tail flick latency; however, dry hit vapor did not differ. Nicotine vapor inhalation, with and without dry hits, also significantly increased anxiety-like behavior. Adolescent exposure to nicotine vapor resulted in a lasting sensitization to the locomotor effects of nicotine, which was exacerbated by dry hitting. Immunohistochemical analyses confirmed that repeated exposure to dry hit vapor in adolescence significantly increased WFA+ intensity in the central nucleus of the amygdala but not the basolateral amygdala or insular cortex. Overall, these data confirm of dry hit e-cigarette vapor may produce different behavioral responses than nicotine vapor alone in rats during adolescence, and this adolescent exposure causes lasting behavioral consequences. Dry hitting and saturated nicotine in rats may differentially alter extracellular matrix structures and immediate early genes integral to neuroplasticity-related learning and behavior. This may indicate a key mechanism underlying an important vulnerability of naïve or unexperienced e-cigarette usage.

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Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.08/KK5

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIDA-IRP

Title: Sex- and Dose- dependent Behavioral Effects of Acute Subcutaneous Nicotine in Mice

Authors: *X. MIN, Z. YE, S. IKEMOTO;
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Abstract: Nicotine exerts complex effects on emotional and cognitive functions that may vary by dose and sex. However, the behavioral profiles following acute peripheral nicotine administration remain incompletely characterized. In the present study, we systematically evaluated the effects of acute subcutaneous nicotine administration on anxiety-like behavior and spatial memory in male and female mice using the open field test, elevated plus maze (EPM), and object location memory (OLM) task. In the open field test, a high-dose nicotine (subcutaneous injection of 0.6 mg/kg, salt form) reduced the time spent in the center zone in male but not female mice. Consistent with this finding, high-dose nicotine significantly decreased open-arm time in the EPM in male mice, whereas a similar but weaker trend was observed in female mice, suggesting increased anxiety-like behavior in male mice at this dose. In

contrast, a low-dose nicotine (0.02 mg/kg, salt form) modestly increased open-arm time in both sexes compared with saline controls. In the OLM task, nicotine produced dose- and sex-dependent effects on spatial memory. the low-dose nicotine significantly improved spatial memory performance in both male and female mice, as indicated by increased discrimination index scores. In contrast, the high-dose nicotine impaired spatial memory performance in male mice but enhanced spatial discrimination in female mice. These findings demonstrate that acute nicotine administration produces dose- and sex-dependent effects on anxiety-related behavior and spatial memory. The differences observed in behavioral outcomes highlight the need for future investigations into the neural mechanisms underlying nicotine's complex effects on emotional and cognitive processes.

Disclosures: X. Min: None. **Z. Ye:** None. **S. Ikemoto:** None.

Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.09/KK6

Topic: H.08. Drugs of Abuse and Addiction

Support: Intramural Research Program of NIH

Title: Establishing Nicotine Reinforcement Doses in Mice Using a Modified Progressive-Ratio Self-Administration Procedure

Authors: *A. GILLESPIE, Y. ARIMA, X. MIN, B. GETACHEW, L. NICOLAS, Z. YE, S. IKEMOTO;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Intravenous self-administration (IVSA) is the gold standard method used for assessing drug reinforcement. This technique is useful in investigating neural mechanisms involved in reinforcing and addictive effects of substances, including nicotine. However, little is known about effective nicotine doses in positive reinforcement. This study examined nicotine self-administration in mice using a modified progressive-ratio 3 (PR3) schedule with no breakpoint, wherein the response requirement increased by three following each reinforcement, to establish dose ranges that reliably support nicotine reinforcement. Mice were initially trained to respond for food pellets on a fixed-ratio schedule, allowing them to acclimate to the operant task. Following catheter implantation, mice were assigned to either a nicotine group (n = 14) or a saline control group (n = 10). The nicotine group was tested with four doses (100, 50, 25, and 0 µg/kg/infusion) presented in descending order, with each dose tested for three consecutive sessions, while saline controls received saline throughout all sessions. Each infusion of nicotine or saline was paired with a light cue. Nicotine self-administration on the PR3 schedule exhibited a significant inverted U-shaped dose-response function, with the greatest response observed at 25 µg/kg/infusion. Infusions of 25 µg/kg doses were significantly greater than saline, 50, and 100

μg/kg. Saline controls displayed stable responding across sessions, suggesting that the dose-dependent changes in the nicotine group were due to nicotine-specific reinforcement rather than nonspecific operant behavior. Additionally, the nicotine group showed elevated responding for saline infusions compared to the saline only group, suggesting the presence of conditioned reinforcing effects of nicotine-associated cues. These findings demonstrate that 25 μg/kg nicotine doses produce reinforcing effects under the PR3 schedule. This supports the use of this dose for investigating the neural mechanisms underlying nicotine reinforcement in mice.

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Poster

PSTR328: Nicotine Dependence, Reinforcement, and Withdrawal Mechanisms

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR328.10/KK7

Topic: H.08. Drugs of Abuse and Addiction

Support: Dr. Edyth H. Schoenrich Scholarship
NIDA T32 DA043469

Title: Sex Differences in Nicotine Self-Administration Behavior and Neural Responses in Mice

Authors: *C. I. MCQUILLEN[1], R. R. MANSOURI-RAD[1,2], W. MARZILLI[1], A. LEE[1], D. S. MCGEHEE[1,2];
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Abstract: The induction and maintenance of nicotine addiction depend on an interplay between rewarding and aversive effects of the drug. Sex differences in nicotine consumption and cessation are well documented; however, the neural mechanisms remain poorly understood. We hypothesize that sex differences in the balance between aversive and rewarding neural responses to nicotine may underlie these biases. To study this, we developed a real-time two-bottle choice paradigm to continuously monitor interactions 24 hrs/day with nicotine and tartrate control bottles across an ascending-descending concentration series (0, 25, 50, 75, 100, 50 μg/mL). Mice had access to each concentration for four days with the nicotine and tartrate bottle swapping locations every two days. We compared consumption, preference, and interaction timing in male (n=16) and female (n=10) mice. After the full range, including an aversive high dose (100 μg/mL), females showed significantly higher nicotine consumption and preference than males upon returning to a moderate dose (50 μg/mL). Females exhibited a nicotine-specific shift in interaction timing, with increased late-night nicotine engagement, suggesting experience-dependent changes in nicotine seeking behavior in females only. Neural activity in the interpeduncular nucleus (IPN) is implicated in aversive responses to nicotine, and likely regulates intake, but the temporal dynamics of this activity have not been investigated *in vivo*. To assess this, we recorded IPN neuronal activity using fiber optic implants above the IPN where we

virally expressed intracellular Ca^{2+} indicator, GCaMP6s, pan-neuronally in nicotine-naïve male (n=10) and female (n=10) mice. Mice were first exposed to an aversive high nicotine dose (1.5 mg/kg) or a rewarding low dose (0.5 mg/kg), then the alternate dose 24 hours later. Both sexes showed IPN activation following either dose. Males showed significantly greater area under the curve in response to the high dose and prolonged response decay kinetics relative to females. Further, male mice pre-exposed to 0.5 mg/kg showed reduced IPN activation in response to 1.5 mg/kg, while females showed no difference. These findings suggest that differences in nicotine consumption between male and female mice may result from stronger activation of IPN aversion circuitry in males. In addition, our data reveal more profound experience-dependent modulation of IPN activity in male mice following repeated exposure, which may reflect tolerance to the aversive drug effects. Better understanding of factors affecting IPN regulation of nicotine consumption may help identify more effective treatments for nicotine addiction.

Disclosures: C.I. McQuillen: None. **R.R. Mansouri-Rad:** None. **W. Marzilli:** None. **A. Lee:** None. **D.S. McGehee:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.01/KK8

Topic: I.02. Perception and Imagery

Support: NIH R01 NS134655-02
NIH T32 GM086287-17

Title: Neural signatures of conscious tactile perception independent of report

Authors: *A. A. SHARMA[1], R. SENJALIA[1], A. WOODWORTH[1], D. S. JIN[3], S. AERTS[1], D. CORMIER[1], A. KHALAF[2], H. BLUMENFELD[4];
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Abstract: Distinguishing activity driven by behavioral reports from neural activity underpinning subjective experience is a core challenge in consciousness research. Our group previously showed that conscious visual perception activates extensive cortical and subcortical networks even without overt responses, using a no-report paradigm. Whether these signatures reflect modality-general mechanisms is unknown. Tactile perception is suited to test this but is underexplored with whole-brain fMRI. To bridge this gap, we developed a tactile no-report paradigm with an MRI-compatible system delivering calibrated pneumatic taps at threshold. In an out-of-scanner phase (N=21), machine-learning classification of pupillometry, microsaccade, and blink features confirmed reliable physiological signatures of conscious tactile perception. We then acquired fMRI on a Siemens Prisma 3T (TR=1 s, 2 mm isotropic, 6 runs/session) over 2 visits. Participants received bilateral stimulation while reporting on one hand only, enabling

matched report and no-report comparisons. Preprocessing and five-stage denoising followed our established pipeline (gray matter masking, high-pass filtering, motion regression, DVARS/FD censoring). Stimulus-locked BOLD epochs (+/-20 s) were extracted for task-relevant (report) and task-irrelevant (no-report) perceived and not perceived threshold trials. Group analyses in MNI space sampled somatosensory (S1, S2), task-positive network (TPN; intraparietal sulcus, frontal eye field, dorsal anterior cingulate, anterior insula), detection/arousal and salience networks, as well as the default-mode network. Preliminary analyses show increased BOLD signal across broad areas of the brain for perceived versus not perceived tactile stimuli. Ongoing work will analyze BOLD signals for the classified no-report perceived and not perceived stimuli to identify report-independent brain areas for tactile conscious perception. These findings will help shed light on cortical and subcortical networks underlying conscious awareness of sensory stimuli across modalities, extending from vision to touch.

Disclosures: A.A. Sharma: None. **R. Senjalia:** None. **A. Woodworth:** None. **D.S. Jin:** None. **S. Aerts:** None. **D. Cormier:** None. **A. Khalaf:** None. **H. Blumenfeld:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.02/KK9

Topic: I.02. Perception and Imagery

Title: Decoding the neural representation of visual spatial location with and without conscious perception

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Abstract: Spatial location is a fundamental feature of visual conscious experience, yet the neural mechanisms supporting spatial recognition with and without conscious perception remain unclear. To address this question, we analyzed fMRI data from a visual threshold perception task in which face stimuli were briefly presented in one of four screen quadrants. Stimulus contrast was individually adjusted to each participant's perceptual threshold so that the participant perceived the stimulus 50% of the time. Participants reported whether they saw the face and identified its quadrant location at the end of each trial. Trials were categorized as perceived when participants reported seeing the face and correctly identified its location, and as not perceived when participants reported not seeing the face and failed to identify the correct quadrant. We focused on decoding stimulus position for faces shown on the left versus right side of the screen under perceived and non-perceived conditions. We used two sources of information derived from preprocessed fMRI data, trial-wise beta weights and BOLD percentage change. More specifically, for the four conditions (left-perceived, right-perceived, left-not perceived, right-not

perceived), a general linear model was used to calculate the beta weights. In parallel, BOLD percent signal change was calculated at 0s, 2s, 4s, and 6s relative to face onset, using the average BOLD response across the whole run as the baseline. We then applied whole brain searchlight decoding to test whether multivariate patterns contained information sufficient to discriminate left versus right stimulus location for both signals. Group-level statistical analysis was then performed to identify brain regions where location information was decodable across participants while controlling family-wise error. For perceived stimuli, we found that the searchlight decoding derived from beta weights and percent change maps included the primary visual cortex and visual association cortex (accuracy > 50%, $p \leq 0.05$). Interestingly, the results from percentage change also showed decoding in the cerebellum. For not perceived stimuli, both maps showed much smaller decoding clusters in scattered cortical and subcortical regions without clear functional significance. These findings suggest that spatial information about visual stimuli is encoded in specific brain areas for consciously perceived stimuli, whereas not perceived stimuli have much weaker encoding of spatial location. Together, these results provide new insights into the spatial representation of visual signals in the brain as modulated by conscious awareness.

Disclosures: J. Qu: None. **A. Khalaf:** None. **S.I. Kronemer:** None. **H. Blumenfeld:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.03/KK10

Topic: I.02. Perception and Imagery

Support: National Institute of Mental Health Intramural Research Program ZIAMH002783

Title: Residual visual conscious perception in cortical blindness: A multimodal neuroimaging case study

Authors: *S. I. KRONEMER[1], C. M. LEVESQUE[3], G. EDWARDS[4], J. FASKOWITZ[5], L. TURTZO[6], B. RISPOLI[7], T. T. LIU[8], J. GONZALEZ-CASTILLO[2], P. BANDETTINI[2]; [2]Section on Functional Imaging Methods, [1]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]NIH, Washington, DC; [4]Lab. of Brain and Cognition, NIH, Bethesda, MD; [5]Psychological and Brain Sci., NIH, BETHESDA, MD; [6]Acute Cerebrovascular Diagnos. Unity, NIH/NINDS, Bethesda, MD; [7]Georgetown Univ., Washington, DC; [8]Neurol., Natl. Inst. of Mental Hlth. Div. of Intramural Res., Washington DC, DC

Abstract: Damage in visual sensory brain regions can cause cortical blindness. Some people with cortical blindness experience impaired or residual conscious vision. Understanding the neurophysiological basis of residual vision in cortical blindness is valuable to study secondary visual pathways and the neural mechanisms of visual conscious perception. Here, we report a case of a person with cortical blindness (right homonymous superior quadrantanopia) who

experiences a unique residual vision: a “sensation” but without the phenomenology of healthy sight. To study the neural basis of this “feeling of seeing”, the participant was shown images in both his sighted and blind visual fields while recording MEG, fMRI, eye tracking, and pupillometry. After each stimulus presentation, the participant was asked to rate the vividness of their visual perceptual experience. Image-evoked brain magnetic fields in the sighted visual field were observed by 100 ms post-stimulus on the posterior scalp. Meanwhile, distinct patterns of magnetic fields were recorded in the blind field, including delayed responses relative to the sighted field and sustained changes in right frontal scalp areas. In the sighted field, time-frequency analyses indicated a sequence of changes: (1) increases in delta and theta power (100-250 ms), (2) decreases in alpha and beta power (250-750 ms), and (3) increases in alpha and beta power (750-1250 ms). In the blind field, only alpha and beta power decreases were observed (500-1500 ms). Next, we explored the relationship between magnetic fields and the participant’s reported vividness of residual vision on a stimulus-level basis. We found a positive correlation between fields and residual vision vividness in frontal scalp regions (300-1100 ms), and a negative correlation with theta and alpha power (500-1500 ms). fMRI findings showed that sighted visual field images evoked expected BOLD responses in the contralateral V1 relative to its presentation location and activations in bilateral higher order regions (e.g., lateral occipital cortex [LOC]). Blind field images also activated surviving contralesional cortex in homotopic regions of the lesioned site, as well as bilateral LOC. In addition, the blind field stimuli evoked responses in brain regions that were not observed in the sighted field, including the right dorsal lateral prefrontal cortex. Together, these results suggest contrasting neural processing for images shown in the blind versus sighted visual field. These distinct signal dynamics may underly the disparate visual conscious experiences linked with healthy versus residual vision in cortical blindness.

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Poster

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Program #/Poster #: PSTR329.04/KK11

Topic: I.02. Perception and Imagery

Support: National Institute of Mental Health Intramural Research Program ZIAMH002783

Title: Investigating perceptual reality monitoring in the healthy brain using an innovative afterimage paradigm

Authors: *C. LEVESQUE[1], S. I. KRONEMER[2], P. J. MOLFESE[3], N. DIJKSTRA[4], P. BANDETTINI[2];
[1]Univ. Col. London - NIMH, London, United Kingdom; [2]Section on Functional Imaging

Methods, Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Section on Functional Imaging Methods, NIMH/NIH, Washington, DC; [4]Univ. Col. London, London, United Kingdom

Abstract: Perceptual reality monitoring (PRM) is our ability to distinguish between real versus imagined perceptual conscious experiences (e.g., seeing versus imagining an object). PRM errors are common in certain patient groups (e.g., schizophrenia or Charles Bonnett syndrome) but are rarely experienced in healthy individuals. The neural mechanisms of PRM remain poorly understood, in part, due to the difficulty of inducing PRM errors under controlled experimental conditions. To address this methodological limitation, we developed a novel PRM paradigm that utilizes afterimages - an illusory visual conscious perception that occurs following an inducing stimulus - and on-screen images designed to mimic the appearance of afterimages, including similar opacity, shade, and presentation duration. EEG was recorded continuously (256 electrodes; 1000 Hz) while 30 healthy adults (9 male) performed our perceptual discrimination task. Participants were informed that afterimages and on-screen images would appear throughout the task, and their goal was to distinguish between which type of percept they were experiencing on a trial-by-trial basis. Because the afterimage inducer would otherwise serve as a predictive cue for the afterimage trials, continuous flash suppression (CFS) was used to suppress the inducer from awareness while preserving the afterimages that followed. After each trial, participants were asked to indicate: (1) whether they perceived an afterimage or image, (2) their response confidence to (1), and (3) the location where either the afterimage or image appeared in their visual field. Behavioral findings reveal that participants confused afterimages for images (~29% error) and images for afterimages (~40% error). Additionally, there was large individual variability in accuracy performance; with some participants being correct almost always and others incorrect. Notably, participants reported greater confidence for correct versus incorrect percept judgements. Participants were more likely to respond they perceived an on-screen image when the image was brighter. Conversely, dim images were more often reported to be afterimages. This result highlights a strategy of using perceptual vividness or strength to judge between afterimages and images. Currently, EEG analyses are underway to investigate the neural processes linked with successful and erroneous PRM.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

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Program #/Poster #: PSTR329.05/KK12

Topic: I.02. Perception and Imagery

Support: NIH Grant ZIA MH002588
NIH Grant P20GM109097

Title: A cross-modal study of the semantic dimensions underlying food similarity judgments

Authors: *J. AVERY[1], C. Y. ZHENG[2], C. CANDY[3], A. PERSICHETTI[4], A. MARTIN[5]; [1]Anat. and Cell Biol., Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK; [2]Natl. Inst. for Mental Hlth., Bethesda, MD; [3]NIMH/NIH, Bethesda, MD; [4]MRRI, Moss Rehabil. Res. Inst., Elkins Park, PA; [5]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Food is a biologically important object category, but the properties that make foods meaningful such as taste, healthiness, and cultural relevance, are not reducible to visual appearance or nutritional content. In the present study, we performed a large-scale behavioral experiment to identify the semantic properties that structure food concepts. We recruited 441 online participants to complete an odd-one-out triplet task using 68 foods presented either as photographs or written names. We applied a sparse non-negative embedding model to the triplet data from both tasks to recover the latent dimensions that best explained the food similarity judgments. We then compared the image and word embeddings to distinguish food dimensions shared across presentation formats from those specific to photographs or words. This process identified nine consensus dimensions shared across image and word datasets, including dimensions related to taste, healthfulness, and broad distinctions among food types. These consensus dimensions accounted for nearly all predictable triplet behavior, outperforming models based on objective macronutrients, image statistics, and general object-property embeddings (all p-values < 0.001). The dimensions showed interpretable relationships with a set of independently collected food property ratings (n=303 participants) and nutritional content, and showed partial overlap dimensions from the broader THINGS object-property space. Out-of-sample validation showed that the same dimensions generalized to an independent food similarity dataset, predicting food triplet choices at 95% of native model performance. Finally, we examined the contributions of consensus dimensions across distinct types of triplet judgments and compared the consensus model to cluster-based and low-dimensional models of food similarity. These analyses revealed that food similarity is not well described as a strictly low-dimensional space or a tree-like hierarchy. Instead, broad dimensions capture coarse distinctions among food types, while finer-grained dimensions discriminate both within and across those divisions. These findings suggest that food knowledge is organized by a multi-scale dimensional structure that is stable across presentation format, partly shared with general object cognition, and enriched by food-specific distinctions.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

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Program #/Poster #: PSTR329.06/KK13

Topic: I.02. Perception and Imagery

Title: A neural mechanism underlying the hierarchical construction of self-generated compositional imagery

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Abstract: Mental imagery enables voluntary generation of internal representations beyond direct perception. However, how the brain compositionally constructs self-generated imagery remains largely unclear. Here, participants played a Tetris-like game during fMRI, either mentally combining two shape features into an object with a predetermined contour (cue-induced imagery), or volitionally deciding which shapes and/or objects to imagine (self-generated imagery). This design allowed us to separate processes for self-generating features and objects. Using logistic regression models to quantify the contributions of current cues, prior biases, and previous choices to behavioral outcomes, we revealed independent sources for self-generated imagery of objects and features, with object generation primarily influenced by previous choices and feature generation predominantly influenced by prior biases. Neurally, Subregions in the frontoparietal and default mode networks showed increased activity that scaled with self-generation demands. Whole-brain decoding searchlight analyses further revealed distinct regions representing self-generated and cue-induced content. Superior representation of self-generated objects was observed primarily in the PFC, including dorsomedial (dmPFC) and anterior lateral PFC (alPFC). In contrast, feature representations engaged a distributed cortical network unaffected by self-generation demand. These findings indicate a dissociation of self-generated imagery for objects and features, both behaviorally and neurally: voluntary construction of self-generated imagery relies primarily on the PFC to assemble high-level object representations, whereas the manipulation of compositional features recruits a common imagery network.

Disclosures: S. Zhao: None. **Q. Yu:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

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Program #/Poster #: PSTR329.07/KK14

Topic: I.02. Perception and Imagery

Support: NSF GRFP

Title: Total daily dopamine dose predicts beat perception ability in Parkinson's disease

Authors: *B. YOSEF, B. BALAMURUGAN, M. MIURA, K. CROSS;
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Abstract: Parkinson's disease (PD) is associated with loss of nigrostriatal dopamine neurons. The basal ganglia are believed to be involved in beat perception, possibly through a role in predictive processing. Dopamine is a candidate mechanism given its function in encoding temporal prediction error and prominence in basal ganglia circuitry, but prior studies are mixed

on the effects of dopaminergic medication on beat perception ability (e.g., Cameron et al., 2016). We conducted an online study in PD patients (n=55) and matched controls (n=53). Participants performed a musical beat perception task, the Beat Drop Alignment Test (BDAT; Cinelyte et al., 2022). They also completed a non-timing control task measuring musical pitch perception, the Mistuning Perception Test (MPT; Larrouy-Maestri et al., 2019). We identified a double dissociation: daily dopamine dose was associated with beat perception ($r=.40$, $p=.003$) but not pitch perception ability ($r=.13$, $p=.361$), while musical background was associated with pitch perception ($r=.55$, $p<.001$) but not beat perception ability ($r=.16$, $p=.236$). Results remained consistent when controlling for disease duration and age. This dissociation suggests the effect of dopamine is specific to beat perception and not reflective of generally improved cognition. Differences between low- and high-dopamine PD groups were driven specifically by on-beat trials as opposed to off-beat trials, suggesting dopamine may particularly support precision of the internal beat representation. Notably, high-dopamine PD patients outperformed both low-dopamine PD patients and age-matched controls. Finally, time since the recent dose had no relationship with beat perception ability. Together, these findings suggest that dopamine is associated with enhanced beat perception ability in PD, potentially through its role in predictive timing mechanisms. These findings highlight the importance of reporting and accounting for dopamine dose when examining timing ability in PD. Given dopamine's role in plasticity at corticostriatal synapses, long-term medication may produce cumulative effects on predictive processing that acute on/off comparisons cannot capture, which may explain the mixed results of prior on/off medication studies.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

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Program #/Poster #: PSTR329.08/KK15

Topic: I.02. Perception and Imagery

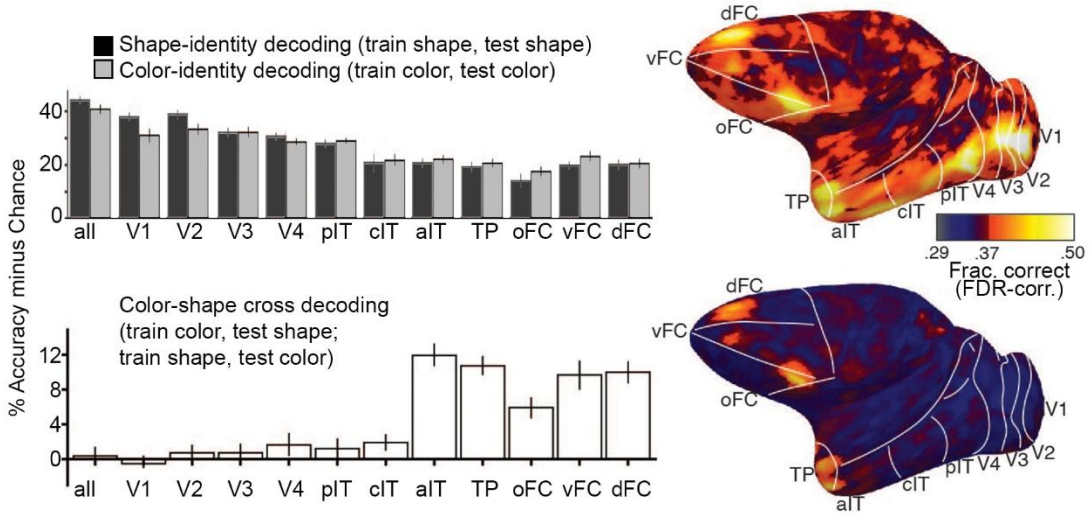
Support: 1ZIAEY000558

Title: The representation of visual paired associations across the brain

Authors: S. R. LOGGIA[1,2], H. E. FEIBES[1], ***B. R. CONWAY**[3,4];
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Abstract: The ability to learn stable paired associations is a key aspect of healthy cognitive function, which underwrites the acquisition and use of stable object concepts (such concepts are often defined by the conjunction of different features, e.g. color and shape). Neurophysiological studies have identified “pair-association” neurons in some brain areas, but sampling limitations

have left unknown the spatial extent of the representation of paired associations across the whole brain—this gap in knowledge bears on open questions about the representation of object concepts, visual imagery, and the mechanisms of synesthesia. Among possible hypotheses are that concept ideas are grounded in sensory areas, mediated by an a-modal “hub” in anterior temporal lobes, represented in prefrontal cortex, and/or distributed broadly across the cortex. Here, we addressed the question using macaque monkeys who spent years learning about a set of simple primitive object concepts each defined by a unique color and shape. During fMRI, the monkeys did trials in which they held in mind one feature of a concept (color or shape), cued by the other. Using a novel whole-brain searchlight analysis inspired by convolutional neural networks, we observed cross-feature decoding not in retinotopic cortex (areas implicated in visual perception), but bilaterally in anterior inferior temporal cortex (aIT), the temporal pole (TP), and prefrontal cortex (PFC) (areas involved in visual cognition). Only TP and aIT had response patterns to concept shapes that matched color-space geometry, suggesting these regions play a key role in conceptual representations. Meanwhile, behavioral errors were only strongly decoded from dorsal PFC, confirming its role in decision making. As far as we are aware, the results provide the first whole-brain view of where paired associations of color and shape knowledge are stored, offering a blueprint for how the brain stores and generates object concepts, and they inspire hypotheses about how conceptual representations engage perceptual representations through feedback during vision.



Disclosures: S.R. Loggia: None. **H.E. Feibes:** None. **B.R. Conway:** None.

Poster

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Program #/Poster #: PSTR329.09/KK16

Topic: I.02. Perception and Imagery

Support: NRF Grant RS-2025-00522357

Title: Closed-loop motor-imagery brain-computer interface training reshapes visual-motion perception

Authors: *S. SEO, O.-S. KWON, S.-P. KIM;
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Abstract: Ideomotor and mirror-system accounts hold that perception and action share representational codes, so learning to control a system through motor imagery could reshape how related visual events are perceived. Whether short-term closed-loop brain-computer interface (BCI) training alters cortical processing of abstract visual motion remains largely untested. If an imagined action becomes bound to its visual-motion effect, then afterward merely viewing that motion should re-engage the trained motor representation. We recorded electroencephalography across a two-day random-dot kinematogram protocol in which participants judged whether the dots moved leftward or rightward, once before training on Day 1 and again after training on Day 2. The random-dot motion spanned six coherence levels from 0 to 100 percent, lasted 1.5 seconds, and required a delayed response. The binding manipulation operated in the BCI training between the perception tasks. Across about 180 closed-loop trials per day, the same random-dot motion served as both the BCI feedback the participant drove and the perception stimulus, with left motor imagery driving leftward motion and right motor imagery driving rightward motion, so each imagined action was paired with a congruent visual-motion effect. A subject-specific decoder built from filter-bank common spatial patterns and a shrinkage linear discriminant analysis read left versus right motor imagery in real time. Once participants reliably controlled the random-dot motion through motor imagery, we compared neural responses recorded during the perception tasks before and after training. The most consistent change was reduced frontocentral anticipatory motor preparation. Sustained frontal slow-wave and premotor activity also fell, together forming a coherent frontocentral motor-preparation signature. The most direct test of binding came from the decoder itself, applied unchanged to the perception recordings: after training, the decoder output shifted toward the direction-matched motor code, the only direction-specific marker, pointing to the viewed motion, reactivating the trained motor pattern. Early visual encoding and frontocentral theta trended similarly but less consistently, and we report them as exploratory. Read together, these before-and-after changes form a candidate signature of training-related plasticity in the perception-action circuit and offer a test of whether closed-loop BCI training recalibrates perception-action coupling.

Disclosures: S. Seo: None. **O. Kwon:** None. **S. Kim:** None.

Poster

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Topic: I.02. Perception and Imagery

Support: Biotechnology and Biological Sciences Research Council (BBSRC) BB/V003917/1
Biotechnology and Biological Sciences Research Council (BBSRC) UKRI2952

Title: EEG decoding during imagery in Aphantasics and Visual Imagers

Authors: *C. L. SCRIVENER[1], J. A. TEED[2,1], E. H. SILSON[1];
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Abstract: The ability to picture something in the 'minds-eye' may seem easy to some, but a proportion of people report a lack of visual imagery in a phenomenon known as 'Aphantasia'. Although several functional magnetic resonance imaging (fMRI) studies indicate differences in the responses measured between typical imagers and Aphantasics, there is little work comparing the time course of visual imagery between groups. We used Electroencephalography (EEG) to compare the imagery time course in Control participants to those with Aphantasia (n=31 in each group). Participants completed a cued imagery task during EEG recording, where they were asked to think about and visualise personally familiar People and Place stimuli. This task is known to elicit strong category selective activation in typical imagers during both fMRI and EEG recordings. They also completed a perception task, where they were simply asked to view repeated images of their personally familiar stimuli. First, we used a searchlight multivariate pattern analysis (MVPA) to ask which channels contained Category information through time (People or Place imagery). In Controls, the strongest category representations were in visual and fronto-central electrodes, with slightly higher decoding in the left hemisphere. In Aphantasics, representations were found in visual and parietal electrodes, with higher decoding in the right hemisphere. Group effects were therefore found in right visual electrodes and left fronto-central electrodes. This could reflect a lack of integration between visual and parietal memory networks in Aphantasics. This may also link to the lack of phenomenological experience of imagery in Aphantasics, given that visual cortex activity may be insufficient to support conscious experience. Next, we aimed to quantify how 'perception like' the EEG signal was during both perception and visual imagery in both groups. To test this, we ran the participants' images through an image computable model ('gist') to quantify the visual differences between them. We hypothesised that if participants were creating a visual representation of their stimuli during imagery, then stimuli with more visual similarities will also be more similar in their EEG response (and vice versa). In perception, the gist model correlated with the EEG signal at similar times in both groups (Controls: 100-300ms, Aphantasics: 100-340ms). During imagery, correlations occurred around 500ms for Controls, but later in Aphantasics (mixed evidence from 1300ms). This suggests that while some 'perception-like' imagery was present in Aphantasics, it was delayed compared to Controls.

Disclosures: C.L. Scrivener: None. **J.A. Teed:** None. **E.H. Silson:** None.

Poster

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Program #/Poster #: PSTR329.11/KK18

Topic: I.02. Perception and Imagery

Support: BBSRC: UKRI2952

Title: Elucidating visual Imagery in Aphantasia: An integrative synthesis of neural dynamics and linguistic phenotyping

Authors: *E. H. SILSON, C. SCRIVENER;
Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: Visual mental imagery, picturing something in your 'mind's eye', is a ubiquitous feature of human cognition. Despite this ubiquity, experiences of mental imagery vary greatly from extremely vivid (i.e., hyperaphantasia), to non-existent (i.e., aphantasia). Prior work on aphantasia has capitalized largely on the spatial resolution of functional magnetic resonance imaging (fMRI) measurements, revealing both preserved and reduced/altered decoding of imagery content (i.e., orientated gabors) in early visual cortex of aphantasics, and reduced patterns of functional connectivity between visual and frontal/temporal cortices. But visual imagery, is not spatially static but evolves dynamically over time. There is a paucity of research regarding the spatiotemporal dynamics of visual imagery in aphantasia. Here, we provide the first detailed measurements of high-level (i.e., people and places) visual imagery dynamics in aphantasia using electroencephalography (EEG). Against expectations, we were able to decode the imagined category throughout the imagery period from the pattern of EEG response in aphantasia. Despite this, large individual variation in the spatiotemporal dynamics of imagery decoding were evident. To better capture this variability, we leveraged both the spatiotemporal dynamics of EEG responses and individualized transcriptions of the imagery experiences using large language models (LMMs). First, key cognitive dimensions of imagery experience in aphantasia were identified in a large independent corpus of aphantasic narratives. Second, these linguistic signatures were found to be present within the individualised transcripts, differentiating between aphantasic individuals at a granularity not possible via the VVIQ. Finally, synthesising the neural and linguistic signatures in aphantasics revealed differential spatial patterns of decoding across space and time. Specifically, we found that aphantasics whose individual narratives were best captured by zero-shot LLM classification of aphantasic language were associated with increased decoding in left-posterior channels early in the imagery period with a weakening over time. In contrast, individual narratives best captured by inner voice/auditory imagery LMM classification were associated with increased decoding in right anterior and posterior channels that increased over time peaking late into the imagery period. These data show the explanatory power of individualised linguistic signatures to explore individual differences in brain dynamics and provide new avenues for exploring the neural basis of mental imagery and human cognitive diversity more broadly.

Disclosures: E.H. Silson: None. **C. Scrivener:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.12/KK19

Topic: I.02. Perception and Imagery

Support: National Research, Development and Innovation Office of Hungary (K-143084)

Title: Neural Signatures of Imagery Ability: Beta-Band Connectivity Modulation During Mental Imagery

Authors: *Á. WELKER[1,2], M. SZAKÁCS[3,1], T. BERJAGA-BUISAN[4], I. KOVÁCS[5,3]; [1]Div. of Mental Hlth. Sci., Semmelweis Univ. Doctoral Sch., Budapest, Hungary; [2]HUN-REN Res. Ctr. for Natural Sci., Budapest, Hungary; [3]HUN-REN-ELTE-PPCU Adolescent Develop. Res. Group, Budapest, Hungary; [4]Computat. Neurosci. Group, Ctr. for Brain and Cognition, Dept. of Engin., Univ. Pompeu Fabra, Barcelona, Spain; [5]Fac. of Educ. and Psychology, Eötvös Loránd Univ., BUDAPEST, Hungary

Abstract: Mental imagery ability varies widely across individuals, yet its neural mechanisms remain poorly understood. The aim of our study was to investigate the neural correlates of mental imagery by analyzing cortical functional connectivity in healthy adults. We examined functional connectivity in HD-EEG recordings using the debiased Weighted Phase Lag Index (dWPLI). Three 5-minute measurements were recorded: during the open-eye resting state, the closed-eye resting state (EC), and during an imagery task (IM), in which participants were asked to imagine and mentally animate a landscape. Imagery-modulated connectivity (IMC) was calculated as the difference between dWPLI(IM) and dWPLI(EC) across frequency bands (delta (1 Hz - 4 Hz), theta (4 Hz - 8 Hz), alpha (8 Hz - 13 Hz), beta (13 Hz - 30 Hz), gamma (30 Hz - 40 Hz)). Six regions (Frontal, Central, Parietal, Left Temporal, Right Temporal, Occipital) were defined for the analysis. Imagery ability was measured using the Vividness of Visual Imagery Questionnaire (VVIQ) and an imagery priming paradigm based on no-report optokinetic nystagmus under binocular rivalry (BR-OKN). From BR-OKN, we calculated an Imagery Priming Effect (IPE) index, which indicates the extent to which the imagined stimulus influences subsequent perceptual processing. We found a significant correlation between IPE and IMC exclusively in the beta frequency band. The correlations persisted within the central region, as well as for the central-frontal, central-parietal, central-left temporal, and left temporal-parietal connections, following correction for age and gender, and for multiple comparisons within the frequency band. No significant correlations were found in the other frequency bands and connections. VVIQ scores did not show a significant association with connectivity measures. Our results suggest that beta-band functional connectivity may play an important role in visual imagery. Although IPE and VVIQ correlated with each other, only the IPE predicted beta-IMC, suggesting that objective behavioral measures capture the neural basis of imagery ability more sensitively than self-report alone.

Disclosures: Á. Welker: None. **M. Szakács:** None. **T. Berjaga-buisan:** None. **I. Kovács:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.13/KK20

Topic: I.02. Perception and Imagery

Title: Rotating Faces in the Mind's Eye: Investigating the Face Inversion Effect

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Abstract: Background: Face perception is highly dependent on orientation, with upright faces typically processed holistically through configural processing, whereas inverted faces rely more heavily on feature-based processing. This phenomenon, known as the Face Inversion Effect, results in slower and less efficient face recognition when faces are presented upside down. Previous research has also demonstrated that increasing rotational angles impair mental rotation performance, even for embodied stimuli such as faces. **Objectives**: The present study examined the effects of facial orientation, face age, and laterality on performance in a face laterality judgment task. We hypothesized that performance would decline as rotational angle increased, with the greatest impairment observed for inverted faces. **Methods**: Thirty-three young adults viewed young and old faces presented at four orientations (0°, ±30°, and 180°) and indicated whether a dot appeared on the left or right side of each face while response times were recorded. **Results**: A significant main effect of orientation was observed ($F(1.46, 46.70) = 7.23$, $p = .004$).Post hoc analyses revealed significantly slower responses to inverted faces (180°) compared to faces presented at 0° ($p = .028$) and -30° ($p = .046$). **Conclusions**: Inverted faces (i.e., 180°) were associated with slower response times, supporting theories that upright faces benefit from holistic processing while inverted faces rely more heavily on less efficient feature-based strategies.

Disclosures: A. Saran: None. **J.J. Marotta:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.14/KK21

Topic: I.02. Perception and Imagery

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Title: Right hippocampal ripples in human precede problem-solving insight

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Abstract: Insightful problem solving often culminates in an abrupt awareness of a solution, but the fast hippocampal dynamics leading up to this transition remain poorly understood in humans. We recorded intracranial local field potentials from hippocampal depth electrodes in 10 patients with drug-resistant epilepsy while they performed two nonverbal reasoning tasks from the WAIS: Matrix Reasoning and Picture Completion. Participants pressed a button at the moment they became aware of a solution and then provided their answer, allowing neural activity to be aligned to subjective solution awareness rather than to stimulus onset or answer production.We operationally defined hippocampal ripples as short periodic oscillations in the 80-140 Hz band and detected events in bipolar hippocampal recordings using amplitude, duration, peak-frequency, and cycle-count criteria. After excluding recordings with interictal epileptiform discharges and artifact-contaminated channels, we analyzed 8,372 ripple events across 54 hippocampal channels. Ripple rates were computed in 500-ms bins from -4 to +4 s around the button press and compared with surrogate ripple-rate traces using FDR-corrected statistics. In both tasks, correct trials showed a significant increase in ripple rate in the right hippocampus during the seconds immediately surrounding solution awareness, beginning before the button press and extending slightly afterward. This modulation was observed from approximately -1.5 to +0.5 s in Matrix Reasoning and -2.0 to +0.5 s in Picture Completion. No significant modulation was observed in the left hippocampus or on incorrect trials. These findings show that right hippocampal ripple events rise before the behavioral report of solution awareness, suggesting that rapid hippocampal dynamics may contribute to the retrieval or recombination of representations that support insight during human problem solving.

Disclosures: K. Yamashiro: None. **T. Yanagisawa:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.15/KK22

Topic: I.02. Perception and Imagery

Support: NSF 2050833

Title: Task Demands Recruit Early Face-Processing Mechanisms into Categorical Decisions: EEG Evidence fom Face Pareidolia

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[1]Univ. of Nevada, Reno Integrative Neurosci. Grad. Program, Reno, NV; [2]Psychology, Univ. of Nevada, Reno, Reno, NV

Abstract: The N170 is widely interpreted as a neural marker of structural face encoding — an early, automatic response to face-like configurations that precedes categorical decision-making. We tested this assumption using face pareidolia, which isolates face-selective neural responses to stimuli that are physically object-like but perceptually face-like. In two experiments using identical stimulus sets of real faces, pareidolia faces, and matched objects, participants either passively viewed stimuli or made speeded category judgments. Real faces elicited the largest N170 response across both experiments, but the N170 response to pareidolia faces was strongly task-dependent: Passive viewing produced no reliable differentiation from objects, while speeded categorization produced a graded effect where pareidolia faces fell in-between faces and objects. This pattern was also observed in behavioral response times. Time-resolved decoding showed that category information emerged early and overlapped with the N170 time-course, while representational dissimilarity analyses revealed a wholesale, task-dependent reorganization of the neural geometry across stimulus categories. These findings suggest that the N170 is not a fixed face-template detector but instead reflects dynamic categorical decisions modulated by task demands. Thus, face pareidolia provides a sensitive probe of the conditions under which early visual cortex commits to a face percept, with broad implications for models of categorical face processing.

Disclosures: A.K. Thoksakis: None. **E.F. Ester:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

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Program #/Poster #: PSTR329.16/KK23

Topic: I.02. Perception and Imagery

Support: NSF 1734907
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NIH R01MH132225

Title: The Neural Correlates of Gaze and Conversation in Real-World Social Interactions Revealed by Intracranial Electroencephalography

Authors: *I. YU[1], A. ALREJA[4], M. WARD[5], T. J. ABEL[2], A. S. GHUMAN[3];
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Abstract: Understanding how the brain integrates dynamic visual and auditory information from faces and voices during real-world social interactions remains a central challenge in cognitive neuroscience. Much of our current knowledge about the brain regions involved in face and voice processing comes from highly controlled laboratory experiments. Intracranial EEG (iEEG) recorded during unconstrained real-world interactions offers a powerful approach to validate these laboratory findings and uncover novel dynamics, despite increased noise and

complexity.To examine the neural dynamics of gaze and conversation, we synchronized iEEG recordings with wearable eye-tracking glasses during real-world social interactions. Subjects wore eye-tracking glasses while iEEG was continuously recorded. We analyzed eye-tracking and auditory recordings to identify when participants fixated on conversation partners or elsewhere, and cross-referenced these instances with whether the partners were speaking or not. This defined four conditions that were time-aligned with the neural signals. We performed four-way classification of multisensory social interaction events, achieving ~56% accuracy (versus 25% chance level, $p < 0.001$). The analysis revealed strong contributions from cortical areas involved in visual and auditory social processing. We validated these findings by examining average response potentials and broadband high-frequency activity for each of the four conditions, which showed clear separation in electrodes from visual and auditory social processing regions (superior temporal gyrus, supramarginal gyrus, fusiform gyrus, and lateral temporal areas). The pattern of contributions from these regions varied depending on the specific condition. These findings demonstrate the feasibility of real-world audiovisual iEEG paradigms and highlight distributed neural networks supporting gaze and speech processing in real-world social contexts. This approach complements controlled laboratory studies and enables future investigations into how visual and auditory systems cooperate or segregate during real-world interactions.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

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Program #/Poster #: PSTR329.17/KK24

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Title: THE CELLULAR BASIS OF R1 DEVELOPMENT IN HUMAN VISUAL CORTEX:DENDRITES IN INFANCY, MULTIPHASIC MYELINATION BY CHILDHOOD.

Authors: *C. M. BACMEISTER[1], V. S. NATU[2], A. REZAI[6], S. TUNG[3], C. TYAGI[4], C. LIAO[7], N. WANG[5], H. WU[4], M. F. PAREDES[8], K. GRILL-SPECTOR[3];
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Abstract: How does myelin develop in human visual cortex, and what cellular processes underlie MRI measures of cortical maturation? Quantitative MRI (qMRI) studies suggest that cortical tissue properties change dramatically throughout development, yet the cellular basis of these changes remains poorly understood. Here, we combine postmortem histology, postmortem MRI, and *in vivo* qMRI to characterize myelination and its relationship to longitudinal relaxation rate (R_1) across human visual cortex development. With histology, we quantify myelin basic protein (MBP), oligodendrocyte (OL) lineage cells (Olig2), differentiating OLs (BCAS1), and dendritic arborization (MAP2) in rare postmortem visual cortex samples from 0-25 years. These measurements were compared with R_1 of postmortem tissue and longitudinal *in vivo* qMRI of 121 participants (0-28 years). Visual cortex is unmyelinated at birth despite the presence of OL lineage cells. Myelin emerges at 4-6 months old and is initially sparse, region-specific, and restricted primarily to deep cortical layers. This early phase coincides with a transient increase in differentiating and new myelinating OLs enriched in deep layers, suggesting an infant burst in OL differentiation that leads to generation of myelinating OLs only in deep cortical layer. In contrast, childhood is characterized by widespread myelination across cortex, with prolonged myelin development in high-level visual cortex, revealing two distinct phases of cortical myelination: an infant phase of deep-layer myelination and a childhood phase of extensive cortical myelin growth. R_1 increases robustly across development but follows a trajectory distinct from myelin. During infancy, R_1 increases rapidly despite relatively modest myelin accumulation. Direct comparison of histology and postmortem MRI demonstrates that R_1 is not significantly related to myelin content in infant cortex but instead tracks dendritic arborization. By childhood, however, R_1 is primarily driven by myelin. These results indicate that the cellular determinants of cortical R_1 change across development, with dendrites contributing substantially in infancy and myelin becoming the dominant factor starting in childhood. Together, these findings provide the first multiscale characterization of human cortical myelination across development and establish that cortical MRI biomarkers reflect distinct microstructural processes at different ages. Early deep-layer myelination may support the emergence of visual function, whereas delayed myelination of superficial cortex may preserve plasticity required for prolonged development of higher-order visual behaviors.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.18/KK25

Topic: E.06. Vision

Support: ZIAMH002909
ZIAMH002966

Title: Depth-dependent profiles for non-visual stimuli in the primary visual cortex

Authors: *G. EDWARDS[1], W. EPSTEIN[1], S. LIPETZKY[3], A. SEYDELL-GREENWALD[4], E. P. MERRIAM[6], R. HUBER[7], E. STRIEM-AMIT[5], C. I. BAKER[2];
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Abstract: The primary visual cortex (V1) is commonly associated with visual processing, yet V1 has been shown to be modulated by non-visual inputs such as spoken language (e.g. Seydell-Greenwald et al., 2023) and soundscapes (e.g. Vetter et al., 2015), or cognitive contributors including task difficulty (e.g. Huk & Heeger, 2000) and attention (e.g. Watanabe et al., 1998). To characterize cortico-cortical depth-dependent feedback profiles in V1 originating from non-visual areas, we adopted the auditory language paradigm of Seydell-Greenwald et al., (2023). Human participants listened to blocks of forward speech (e.g. “Birthday cake lights are candles”, “Something that sweeps the floor is a canoe”) and reversed speech through headphones in a 7 Telsa MRI while fixating a central cross. During forward speech, participants pressed a button when a sentence was semantically incorrect. During reversed speech, participants responded when they heard a beep. Using a standard BOLD gradient-echo EPI sequence (n=9), we first replicated V1 activation for forward versus reserved speech, reported by Seydell-Greenwald et al. (2023). We also replicated stronger activation in left V1 compared to right V1, potentially reflecting left lateralization found in the frontotemporal language network. Next, we employed the Vascular Space Occupancy (VASO) sequence to characterize the non-visual depth-dependent response profile of V1 using the same paradigm (n=13). Forward speech elicited modulation in superficial and deep compartments, whereas reversed speech modulated only superficial compartments. Crucially, we contrasted our non-visual depth-dependent response with a visual checkerboard response profile and found modulation of the middle compartments. These findings support the commonly hypothesized mid-depth activation during feedforward stimulation, and superficial/deep modulation for feedback. In animal models, cortico-cortical feedback of auditory stimuli to V1 has been demonstrated in both superficial and deep layers (e.g. Oude Lohuis et al., 2024). Here, both our auditory conditions modulated superficial compartments, while deeper modulation was only observed during forward speech, potentially reflecting language-related feedback. However, because task demands differed between conditions, contributions from task difficulty or attention cannot be excluded.

Disclosures: G. Edwards: None. **W. Epstein:** None. **S. Lipetzky:** None. **A. Seydell-Greenwald:** None. **E.P. Merriam:** None. **R. Huber:** None. **E. Striem-Amit:** None. **C.I. Baker:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.19/KK26

Topic: E.06. Vision

Support: ZIAMH002966
ZIAMH002909

Title: Eye metrics during fixation not modulated by spoken language comprehension

Authors: *W. EPSTEIN[1], G. EDWARDS[2], S. LIPETZKY[4], A. SEYDELL-GREENWALD[5], E. MERRIAM[7], R. HUBER[8], E. STRIEM-AMIT[6], C. I. BAKER[3];
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Abstract: In congenitally blind individuals, primary visual cortex (V1) has been shown to increase in activity during speech comprehension, providing evidence for cross-modal plasticity in V1. However, the same activation has been found in sighted individuals (Seydell-Greenwald et al., 2023), suggesting innate connectivity between V1 and the frontotemporal language network. However, such activation could arise from multiple sources. Beyond cortico-cortical feedback modulation, one potential contributor to V1 activation could be condition-dependent eye movements; eye movements alter visual input to the retina, subsequently influencing V1 activity. In order to determine if spoken language drives condition-dependent eye movements, we analyzed eye-tracking data during a simple language processing task, adhering to the methods of Seydell-Greenwald and colleagues. We presented sighted participants (n=16) with 3 runs of audio recordings of forward and reverse speech in 30-second counterbalanced blocks. In the forward speech condition, participants heard short sentences (e.g., “Birthday cake lights are candles”, “A three-sided shape is a globe”) and were tasked with indicating semantically incorrect statements. In the reverse speech condition, participants heard the same sentences played backwards, and were tasked with reporting a beep that played following some of the reversed sentences. While listening to the speech, participants were instructed to maintain fixation at a cross in the center of the screen. Eye-tracking data was collected using an Eyelink 1000 in two separate sessions: first inside of a 7 Tesla MRI machine (see linked abstract from Edwards and colleagues), and on a later date in a behavioral-only suite. In both eye-tracking datasets, we found no differences in pupil size, gaze position density, fixation drift, or blink rate between the forward and reverse speech conditions. These findings provide evidence that the V1 activation for spoken language does not stem from changes in eye metrics. Rather, the lack of condition-dependent eye movements supports the interpretation that activation for spoken language in V1 can be restricted to feedback modulation from non-visual brain areas.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

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Topic: E.06. Vision

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0204802)
National Natural Science Foundation of China (T2421004, 31930053)

Title: How early visual cortex separates and shares signals for seeing and imagining: a multiplexing mechanism in the human brain

Authors: *R. YANG, G. CHEN, Q. WANG, F. FANG;
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Abstract: Our brain is widely viewed as a prediction machine that generates internal representations supporting imagery, working memory, and planning. This creates a multiplexing challenge for early visual cortex (EVC) in encoding external input while maintaining internally generated content. Neuroimaging studies implicate the intraparietal sulcus (IPS) in maintaining internal representations and providing top-down signals to EVC. Yet, how EVC-IPS interactions shape this multiplexing, and what gates them from moment to moment, remains unclear. We recorded intracranial EEG from EVC and IPS simultaneously in ten epilepsy patients performing a visual imagery task. Participants viewed or imagined a spatially cued oriented line and discriminated its location relative to a probe after a 1-s delay while maintaining fixation. A luminance-detection task using identical displays served as a control. We extracted high-gamma activity (HGA) bursts from local field potentials (LFPs) and found that burst rate in EVC and IPS increased during perception and imagery. To assess inter-areal communication, we identified EVC-IPS burst pairs that co-occurred within ±50 ms and classified them as IPS-leading, EVC-leading, or non-coupled. During imagery, the proportion of coupled bursts increased relative to baseline. Conversely, during perception, IPS-leading bursts decreased during encoding, whereas EVC-leading bursts increased during recall. These reallocations suggest a functional separation between an IPS-coupled EVC subnetwork supporting internal content and a non-coupled subnetwork driven by external input. Next, we tested two candidate mechanisms proposed to reshape inter-areal coordination on short timescales. First, coupled bursts were more strongly phase-locked to low-frequency LFPs than non-coupled bursts across the two areas. Consistent with the frequency-multiplexed account of feedforward and feedback channels, coupled bursts co-occurred with higher theta power and lower alpha/beta power in EVC but the opposite pattern in IPS, indicating coupling occurred when EVC was biased toward feedforward and IPS toward feedback signaling. Second, peri-burst pupil diameter, an index of arousal-linked neuromodulation, was larger for IPS-coupled EVC bursts than for non-coupled bursts. Within IPS, only IPS-leading and non-coupled bursts tracked pupil, indicating that arousal modulates IPS-to-EVC top-down signaling. Together, these findings show that EVC multiplexes external input with internally generated content by switching between subnetworks defined by burst coupling with IPS, illuminating how the brain constructs an internal world model.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

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Program #/Poster #: PSTR329.21/KK28

Topic: E.06. Vision

Support: NIH Grant F32EY036266

Title: Quantifying retinotopic visual features encountered by the visual system during real-world behavior

Authors: *A. SHAFER-SKELTON, M. M. HAYHOE;
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Abstract: Every day, the visual system supports complex behaviors such as spatial navigation and other visually guided actions. To understand how visual cues shape the internal world models supporting these behaviors, it is critical to understand interactions between the visual system and its inputs. For example, real-world visual inputs are shaped by active exploration via eye, head, and body movements that determine where visual information lands on the retinas and how it propagates through the retinotopic (retina-centered) visual system. In turn, cumulative visual experience can even influence the feature selectivity of retinotopic cortex. While some work has analyzed the objects and features participants *fixate* during natural behavior, no previous work has characterized the real-world retinotopic features landing across the wider visual field. Recent open data sets like the VEDB (Greene et al., 2024) have made this possible for the first time by recording eye-tracking data and head-centered video during a range of real-world activities. Here, we used the VEDB to ask how similar the visual features are that land in different parts of the visual field. First, we estimated humans' retinotopic visual inputs by combining real-world eye-tracking with head-mounted video. We then computed mid-level visual features often considered to be V2-like: patterns of orientation and spatial frequency summarized within pooling regions across the visual field (Freeman & Simoncelli, 2011). Next, we created similarity matrices by computing correlations between the average features encountered by each possible pair of pooling regions. Preliminary analyses of these matrices suggested that visual features landing at similar eccentricities are more similar than those at more different eccentricities. Then, we assessed the relative contributions of the visual inputs themselves vs. the modeled structure of the visual system. To do this, we compared matrices computed from real-world retinotopic inputs to those from two control conditions: phase-scrambled versions of the same images and random pixel noise. This revealed strikingly similar matrices across all three input types, arguing that the structure of the modeled visual system played a major role in shaping the similarity of visual features across the visual field. Ongoing analyses will disentangle the roles of spatial-frequency selectivity and pooling-region size in driving the eccentricity effect. This work is a critical step towards understanding how world

models arise from the interplay of (a) the structure of the retinotopic visual system, (b) humans' natural gaze behavior, and (c) the structure of the world itself.

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Poster

PSTR329: Human Perception, Imagery, and Imagination II

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Title: Early visual cortex is not functionally necessary for temporal attention: A TMS study

Authors: *H.-H. LEE[1], M. CARRASCO[2];
[1]Psychology, [2]Psychology and Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: [Background] Temporal attention r prioritizes sensory information at specific points in time. Whereas previous studies have shown that early visual cortex plays an important role when deploying temporal attention and temporal expectation, they conflated these two distinct constructs. Recent psychophysical and MEG studies have disentangled them, identifying potential neural correlates of temporal attention via connectivity and coherence analyses in the visual cortex. However, causal evidence is still lacking. In this study, we used transcranial magnetic stimulation (TMS) to investigate whether early visual cortex is functionally necessary for endogenous temporal attention, while keeping temporal expectation constant. [Methods] Observers performed an orientation discrimination task, while a precue instructed them to attend to one of two sequential grating stimuli-Target 1(T1) or Target 2(T2)-with 100% validity, or to both (a neutral cue). Sub-threshold double-pulse TMS was delivered to V1/V2 during target presentation in one of four conditions: (1) T1, (2) T2, (3) both T1 and T2, or (4) neither; thus, observers could not predict when the pulses would occur. Sensitivity (d′) was quantified using signal detection theory. Reaction time was measured as a secondary variable.[Results] A significant attentional effect emerged across all 4 TMS conditions: d′ was higher and reaction time was faster for valid trials to T1 or T2 than to neutral trials. Critically, there was no interaction between attention and TMS condition. The same pattern held when analyzing accuracy and reaction time together using the balanced integration score (BIS) and inverse efficiency score (IES).[Conclusion] By isolating temporal attention from expectation, our psychophysics-TMS results showed that early visual cortex is not functionally necessary for endogenous temporal attention. These findings parallel the role of V1/V2 in endogenous

(voluntary) covert spatial attention, but contrast with its necessity in exogenous (involuntary) attention. This suggests that whereas V1/V2 are crucial for exogenous spatial attention, they are not functionally necessary for either endogenous spatial or temporal attention. The current findings support the idea that temporal attention and temporal expectation are distinct cognitive processes, with higher-order frontoparietal areas playing a more important role in temporal attention.

Disclosures: H. Lee: None. **M. Carrasco:** None.

Poster

PSTR329: Human Perception, Imagery, and Imagination II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR329.23/KK30

Topic: E.06. Vision

Support: NIH Grant RO1EY030434
NIH Grant P41-EB030006

Title: Distinct Motion- and Disparity-Selective Regions Within Human Scene- and Object-Selective Cortex

Authors: *S. NASR[1,2], A. B. MORLAND[3,4];
[1]Athinoula A Martinos Ctr. for Biomed. Imaging, Charlestown, MA; [2]Radiology, Harvard Med. Sch., Boston, MA; [3]Univ. of York, York, United Kingdom; [4]Radiology, Mass Gen. Brigham, Charlestown, MA

Abstract: Visual scene- and object-selective cortical regions are traditionally defined by their category selectivity. However, growing evidence suggests that many of these regions also respond strongly to visual features such as binocular disparity and visual motion. Despite the importance of these signals for perception and behaviour, their functional organization within category-selective cortex remains poorly understood. Specifically, it is unknown whether motion and disparity are represented by distinct functional regions embedded within scene- and object-selective areas or by overlapping cortical sites distributed across the same area. Using high-resolution fMRI (7T; voxel size = 1 mm isotropic), we mapped motion-, disparity-, and color-selective responses within the retinotopic area V3A, the lateral occipital complex (LOC), and two scene-selective regions, the Posterior Intraparietal Gyrus Scene-selective area (PIGS) and the Occipital Place Area (OPA). Participants included thirteen individuals with normal vision, age = 23-46 years old (5 females). We identified discrete clusters exhibiting preferential responses to either moving (compared to stationary concentric rings) or fine varying disparity (compared to zero disparity based on random-dot stereograms) throughout all examined regions, with minimal spatial overlap between motion- and disparity-selective clusters. Interestingly, while V3A exhibited a balanced representation of motion- and disparity-selective sites, both scene-selective regions contained substantially larger disparity-selective than motion-selective

territories. In contrast, LOC exhibited a more heterogeneous organization: ventral LOC contained a greater motion-selective region, whereas dorsal LOC included a larger disparity-selective region. Color-selective clusters were rarely detected within these regions, in marked contrast to ventral temporal visual areas within the fusiform gyrus. These findings reveal a fine-scale functional segregation of motion and disparity processing across human visual cortex and suggest that feature-selective responses are organized into distinct functional domains embedded within both retinotopic and category-selective visual areas.

Disclosures: S. Nasr: None. **A.B. Morland:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.01/KK31

Topic: I.03. Decision Making

Support: NIH grant R01 MH091068

Title: Default Network-Frontoparietal Control Network Segregation and Delay Discounting in ADHD

Authors: *A. COOPER[1], I. FARNSWORTH[2], P. MUKHERJEE[2], J. BORDEN[2], J. B. SCHWEITZER[2], S. M. MCCLURE[1];
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]UC Davis MIND Inst., Univ. of California, Davis, Sacramento, CA

Abstract: Delay discounting (DD) refers to the decline in the present value of a reward as the delay to its receipt increases. Steeper DD reflects a greater preference for smaller, sooner rewards over larger, later rewards. We investigated differences in DD associated with attention-deficit/hyperactivity disorder (ADHD). We tested whether ADHD-related differences in DD are associated with differences in default network (DN) and frontoparietal control network (FPCN) connectivity. Previous work has separately linked ADHD to altered DN and FPCN connectivity, and related DD to DN and fronto-subcortical connectivity. It remains unknown whether DN-FPCN segregation contributes to elevated DD in ADHD. Participants with ADHD and neurotypical controls completed a monetary DD task, and resting-state fMRI data were collected during the same study visit. DD was quantified using the discount rate, k, which was log-transformed prior to analysis. The DN and FPCN were defined using the Schaefer-200 cortical parcellation assigned to the Yeo 7-network atlas. Average DN and FPCN time series were computed from parcel-wise time series. DN-FPCN connectivity was estimated as the Pearson correlation between DN and FPCN time series and Fisher z-transformed prior to analysis. Correlations between DN-FPCN correlation served as the primary index of segregation, with more negative values indicating greater functional segregation. Group differences in DN-FPCN connectivity were tested between ADHD and neurotypical participants. We then tested whether

DN-FPCN connectivity was associated with log(k). We predicted that ADHD would be associated with reduced functional segregation and that weaker DN-FPCN segregation would be associated with steeper DD. This work may advance understanding of the neural basis of impulsive choice in ADHD by identifying a large-scale network mechanism that supports intertemporal choice.

Disclosures: A. Cooper: None. **I. Farnsworth:** None. **P. Mukherjee:** None. **J. Borden:** None. **J.B. Schweitzer:** None. **S.M. McClure:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.02/KK32

Topic: I.03. Decision Making

Support: L.E. and C.F. contributed equally to this work.

Title: Cardiac phase and exteroceptive priors differentially modulate somatosensory sensitivity, confidence, and autonomic performance monitoring

Authors: *L. ENK[1,2], C. FORSTER[1,3,4], M. GRUND[1], E. AL[5,1], S. POPPE[6,2], A. VILLRINGER[1,2,7,8,9];
[1]Neurol., Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [2]Max Planck Sch. of Cognition, Leipzig, Germany; [3]Bernstein Ctr. for Computat. Neuroscience, Humboldt Univ., Berlin, Germany; [4]Clin. Brain Networks, QIMR Berghofer Med. Res. Inst., Brisbane, Australia; [5]Psychiatry, Columbia Univ., New York, NY; [6]Inst. of Sociology, Leipzig Univ., Leipzig, Germany; [7]MindBrainBody Inst., Berlin Sch. of Mind and Brain, Humboldt Univ., Berlin, Germany; [8]Clin. for Cognitive Neurology, Univ. of Leipzig Med. Ctr., Leipzig, Germany; [9]Charité – Universitätsmedizin Berlin, Berlin, Germany

Abstract: Perceptual decision-making integrates concurrent exteroceptive and interoceptive informational streams. While near-threshold somatosensory detection declines during cardiac systole relative to diastole, it remains debated whether this fluctuation reflects a mere peripheral constraint suppressing sensory sensitivity (*d*'), or involves a flexible interoceptive prior modulating decision criterion (*c*). Using an exploration-validation approach across two independent non-clinical human cohorts (Exp 1, exploration: $N = 42$, 22 female, age = 26 ± 4 years [$M \pm SD$]; Exp 2, pre-registered validation: $N = 39$, 23 female, age = 25 ± 4 years), we manipulated explicit external signal-probability cues (25% vs. 75%) during a near-threshold somatosensory detection task while tracking continuous electrocardiography (ECG) to determine cardiac target-timing and cross-trial dynamics. Participants reported signal presence and subsequent detection confidence (via binary button responses). Linear mixed-effects modeling confirmed that explicit probability cues reliably shifted the decision criterion (*c*) across both experiments. Crucially, validation data demonstrated that the cardiac modulation of detection

performance was statistically invariant across external cueing contexts; instead, the cardiac cycle constrained sensory sensitivity (*d*') independently of exteroceptive expectations, with lower sensitivity restricted to systole. Conversely, cardiac phase and signal probability cueing interacted significantly to shape metacognitive processing of detection performance. This interaction occurred exclusively under high-signal-probability cues, where cardiac diastole at target onset tuned confidence in a cue-congruent manner, elevating confidence on signal-present trials but lowering it during correct rejections. This suggests that the enhanced sensory precision afforded by cardiac diastole facilitates a more effective alignment of subjective confidence with external priors. Finally, explicit expectations and lowered decision confidence robustly and independently drove post-target cardiac deceleration, directly indexing an autonomic signature of performance monitoring. This confidence-related slowing further scaled with pre-target baseline RR duration (28% per within-person SD). Together, these findings reveal a dissociation where the heart sets a rigid boundary on physical signal detection, but acts as a state-dependent modulator for subjective confidence. This confidence coincides with a robust autonomic signature of post-target cardiac deceleration.

Disclosures: L. Enk: None. **C. Forster:** None. **M. Grund:** None. **E. Al:** None. **S. Poppe:** None. **A. Villringer:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.03/KK33

Topic: I.03. Decision Making

Title: Neural signatures of perceived control: Decreased alpha band power in response to cues that predict the level of control during a decision-making task.

Authors: *L. HUANG[1], M. STAEHLING[1], B. ACHORD[1], C. M. HILL[2], D. A. HARRISON[1], D. E. WADDELL[1], A. J. DEL ARCO[1];
[1]Univ. of Mississippi, Oxford, MS; [2]Louisiana State Univ., Baton Rouge, LA

Abstract: Perceived control is the belief that one's actions will produce expected outcomes. Previous studies show that perceived control shapes how the brain processes motivational stimuli (i.e., reward, punishment) and guides decision-making behavior. Moreover, the absence of perceived control is associated with anxiety. Yet it is still unclear how the brain processes the perception of control. The current research utilizes electroencephalography (EEG) to identify neural signatures of perceived control during a decision-making task. Male and female (college students, 18-35 years old, n= 27) participants performed a decision-making task that consisted of 204 trials divided into 6 blocks where they had the opportunity to choose between gaining or losing money by pressing pre-defined keys according to specific stimuli shown on a computer screen. Critically, each trial started with a 3-seconds control-cue that predicted how much control participants had over their choice's outcome. During the first part of the task (60 trials, blocks 1-

3), participants learned to associate the control-cues (circle, triangle and star) with the level of control (high-, moderate- and low-control). Then, the three control-cues were shown pseudo-randomly (144 trials, blocks 4-6). EEG was recorded by using 64 electrodes placed according to the 10-20 system (actiCHamp, Brain Products). Event-related oscillations time locked to control-cues presentation were analyzed for each participant during the task. Participants were asked to rate from 0-low to 7-high how much control they believed they had over their choice's outcome during the task. The results show that participants rated significantly higher (6.7 ±0.2) high-control compared to low- (2.8 ±0.3) and moderate- (3.4 ±0.3) control-cues, confirming they learned to associate cues with level of control. Participants' reaction times were also different depending on the level of control. They were faster during high-control trials (609 ±31 ms) compared to low-control trials (723 ±39 ms) ($t(25)= 4.61$, $p< 0.001$). A time-frequency analysis (blocks 4-6) from electrodes Pz and Fz showed cue-related decreases in alpha band power during the task. However, alpha power decreases lasted longer during low- (Fz: $t(25)= 2.53$, $p= 0.015$) and moderate- (Fz: $t(25)= 3.31$, $p= 0.002$; Pz: $t(25)= 2.46$, $p= 0.021$) compared to high-control-cues. These results suggest that the perception of control is regulated by the power of alpha oscillations, which ultimately might set attentional resources for optimal decision making.

Disclosures: L. Huang: None. **M. Staehling:** None. **B. Achord:** None. **C.M. Hill:** None. **D.A. Harrison:** None. **D.E. Waddell:** None. **A.J. Del arco:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.04/KK34

Topic: I.03. Decision Making

Support: DBT Wellcome Trust IA Fellowship (IA/I/20/2/505204)

Title: Environmental Statistics Reshape Decision Policy and Pavlovian Avoidance through Dissociable Theta and Beta Dynamics

Authors: *P. PRIYANSHU, A. RAMAKRISHNAN;
Biol. Sci. and Bioengineering, Indian Inst. of Technol. Kanpur (IITK), Kanpur, India

Abstract: Pavlovian biases facilitate rapid action selection by coupling appetitive outcomes with approach and aversive with avoidance. Although adaptive in many contexts, these biases can interfere with goal-directed behavior when environmental contingencies change. Frontal-midline theta has been implicated in conflict monitoring and cognitive control, whereas beta-band activity has been linked to action selection and commitment. We hypothesized that environmental conflict suppresses maladaptive Pavlovian avoidance through coordinated changes in theta- and beta-band dynamics. Participants performed a sequential approach-avoidance task with No-Conflict (NCT), Low-Conflict (LCT) and High-Conflict (HCT) reward-punishment trees while EEG was recorded (N=44); conflict frequency varied across blocks to

create low- (B1) and high-conflict (B2) environments. Consistent with prior behavioral findings (N=116), objectively safe NCTs were paradoxically avoided in B1 despite no punishment, and high-conflict environments selectively restored NCT approach (B1: 79.42 +/- 1.18%, B2: 82.52 +/- 1.46%, p=0.019), with the largest improvements in high trait anxious individuals. Decomposing a dominant frontocentral broadband EEG component (PC1; 58.1 +/- 14.9% explained variance; loadings ~0.45 Fz, 0.43 FCz, 0.39 FC1, 0.35 FC2, 0.36 Cz) into theta and beta activity revealed dissociable processes. Post-stimulus but pre-decision theta (-1351 to -1073 ms) showed a robust cluster corrected conflict effect (t = 3.5, p= 0.01) consistent with conflict monitoring whereas pre-stimulus theta (-300 to -200 ms) exhibited anxiety-dependent adaptation (Block×Anxiety F=2.69, p=0.045), high trait anxious individuals engaging more theta in conflict-rich environments. In contrast, late beta (1000-1200 ms post-stimulus; 300-500 ms pre-mean RT) positively predicted trial-by-trial approach (beta=0.169, p=1.35x10^-11) and showed selective environment-dependent shifts for NCTs (B1=0.005, B2=0.105; p=0.048), where behavioral adaptation was strongest. A theta-beta balance metric (pre-stimulus theta minus post-stimulus beta) increased with conflict (F=4.95, p=0.026). Critically, for NCTs this balance shifted from theta-dominant in B1 (+0.017) to beta-dominant in B2 (-0.097), paralleling the selective restoration of the adaptive approach. These findings suggest that environmental conflict suppresses Pavlovian avoidance not solely through enhanced conflict monitoring, but through a reconfiguration of frontocentral neural dynamics that promotes implementation of adaptive approach behavior.

Disclosures: P. Priyanshu: None. **A. Ramakrishnan:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.05/KK35

Topic: I.03. Decision Making

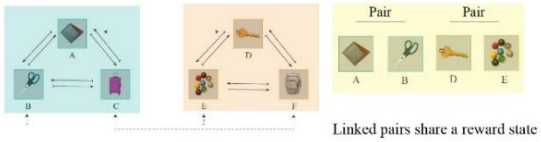
Title: Neural mechanisms for selective credit assignment and generalization in structured reward learning

Authors: *X. ZHONG, S. A. PARK;
Psychology, Virginia Tech., Blacksburg, VA

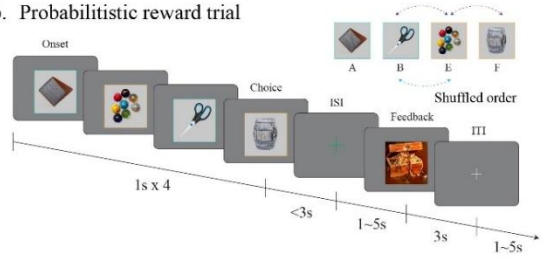
Abstract: Learning from rewards in structured environments requires the brain to determine which experiences should be linked by feedback and which should not. Credit assignment depends on representations that organize experiences by underlying latent structure rather than surface similarity, but the neural basis of this generalization remains unclear. We tested this question with fMRI while participants learned probabilistic rewards for ordered object pairs under reversals (Fig. a-c). Some perceptually dissimilar pairs shared reward contingencies and should be updated together (Fig. a; e.g., AB and DE), whereas perceptually similar pairs could belong to different reward states and should be updated independently (e.g., AB and BA). We

hypothesized two complementary levels of task structure representations. One specifies which pairs should be updated together, allowing feedback from one pair to assign credit to its linked partner. The other tracks which structural system is currently rewarded, allowing adaptation to reversals without storing pair values separately. A Bayesian model explained choices, suggesting that participants used hidden task structure to guide learning (Fig. c). ROI-based RSA suggested complementary representations across learning phases. During feedback, hippocampal patterns showed increased similarity between the chosen pair and its inferred partner, suggesting that feedback may be assigned beyond the directly experienced pair (Fig. d). In state-code RSA, preliminary data showed marginal effects consistent with multidimensional reward-state coding in hippocampus, and with a more compact reward-state code in the prefrontal cortex (Fig. e). Together, these findings suggest that structured reward learning depends on multi-level, separable representations for credit assignment and flexible adaptation.

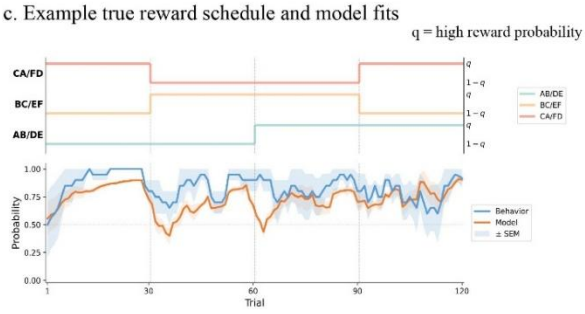
a. Ordered pairs and hidden links



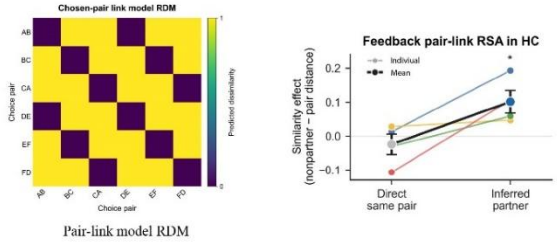
b. Probabilitistic reward trial



c. Example true reward schedule and model fits

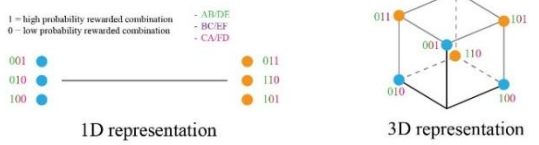


d. Hippocampal patterns reflect inferred pair links during feedback



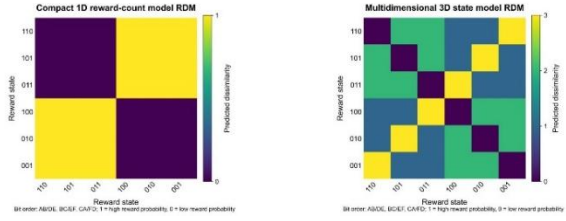
Pair-link model RDM

e. State-code RDM: compact vs multidimensional representations



1D representation

3D representation



Disclosures: X. Zhong: None. **S.A. Park:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.06/KK36

Topic: I.03. Decision Making

Support: Hong Kong Research Grants Council (C5001-23Y)

Title: Causal role of the dorsal anterior cingulate cortex in adaptive choice switching and inferential learning

Authors: *J. Y. TO[1], C.-K. LAW[1], E. FOURAGNAN[4,5], B. K. CHAU[1,2,3];
[1]Dept. of Rehabil. Sci., [2]Univ. Res. Facility in Behavioral and Systems Neurosci., [3]Mental Hlth. Res. Ctr., The Hong Kong Polytechnic Univ., Hong Kong, Hong Kong; [4]Sch. of Psychology, Fac. of Hlth., [5]Brain Res. and Imaging Centre, Fac. of Hlth., Univ. of Plymouth, Plymouth, United Kingdom

Abstract: Decisions in everyday life often require us to forgo alternatives without knowledge of their potential outcomes. Past studies in reinforcement learning typically provided explicit information on counterfactual outcomes, implicating counterfactual learning in areas such as the dorsal anterior cingulate cortex (dACC). However, even if counterfactual outcomes remain unknown, experiencing the outcome associated with the chosen option may prompt inferences about potential outcomes had the alternative options been chosen and drive behavioral changes. Here, we investigated the role of the human dACC in counterfactual learning when alternative outcomes are unknown, in a human functional magnetic resonance imaging (fMRI) experiment (n=33) and a human transcranial ultrasound stimulation (TUS) experiment (n=26). Participants in both experiments performed a decision-making task, where three abstract visual stimuli were included, each associated with a hidden reward probability that changes over the duration of the task. On each trial, participants were shown two stimuli, with the third stimulus being unavailable, and were asked to choose the stimulus that leads to the most reward. Reinforcement learning models fitted to the participants' choice behavior showed that choice behavior is best described with a model that updates the chosen and unchosen option values simultaneously, suggesting that inferential learning is applied selectively to the unchosen option, and not to the unavailable option. The fMRI data showed that chosen and unchosen option learning involved distinct network of brain areas, with unchosen option value encoding found in the dACC. Time course analysis further demonstrated that the dACC encoded the intention to switch to the unchosen option in the next trial. Finally, we analyzed behavioral data from the TUS experiment that involved applying stimulation to the dACC, which is shown to induce neuroplasticity and increase its functional connectivity. By reapplying reinforcement learning models, we found that TUS-dACC altered learning strategy, causing counterfactual learning to be additionally applied to the unavailable option. Together, these findings identify the dACC as a key region in counterfactual learning and guiding adaptive decision-making with partial feedback.

Disclosures: J.Y. To: None. **C. Law:** None. **E. Fouragnan:** None. **B.K. Chau:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.07/KK37

Topic: I.03. Decision Making

Support: NIH grant MH137210
DA29330
NS118463

Title: Persistent choice and outcome signals in the macaque fronto-cortico-striatal network

Authors: *N. H. LAM[1], H. SEO[2], D. LEE[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Yale Univ., New Haven, CT

Abstract: Complex decision making involves multiple areas in the brain orchestrating to compute various signals that lead to decision variables and choices. Understanding how neural activities in various brain areas are coordinated during such transformation is becoming feasible due to advances in experimental apparatus and analysis methods. Game theoretic tasks also enable systemic manipulation of multiple task variables.
We re-analyzed the activity of single neurons recorded from 6 brain areas during a biased matching pennies task. During this task, monkeys made a series of binary choices playing a matching pennies game against computer agent and received tokens (exchangeable with juice whenever the animal accumulated 6 tokens) if the monkey choice matched that of the agent. The task was biased because when the animal lost, the number of tokens remained unchanged and decreased respectively for the two options. The computer agent exploited any reliable patterns in the monkey choice and outcome histories, motivating the animals to choose unpredictably (mixed strategies). We found that the animals' choice reflected multiple variables, including choice history, outcome history, and asset (number of tokens).
Neural activities in the dorsal-lateral prefrontal cortex (dlPFC), dorsal-medial prefrontal cortex (dmPFC), anterior cingulate cortex (ACC), caudate nucleus (CD), ventral striatum (VS), and external globus pallidus (GPe) were recorded while monkeys performed the biased matching pennies task. While all areas contained the multiple variables related to the animal's choice, they differed in the details of encoded signals and hence their potential roles in learning and decision making. For example, choice signal was encoded earlier and more strongly in dmPFC and CD. In all areas, losing a token in the previous trial was represented more robustly than winning one, and this was more common in the cortical areas than the basal ganglia. In addition, GPe was selective to past reward and asset, but encoded other history signals only weakly. Finally, population analysis revealed that the relationship between choice and loss signals is preserved across trials for all areas. These findings suggest that the primate fronto-cortico-striatal network play a key role in integrating multiple task variables across trials during reinforcement learning.

Disclosures: N.H. Lam: None. **H. Seo:** None. **D. Lee:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.08/KK38

Topic: I.03. Decision Making

Support: JSPS KAKENHI Grant Number JP25K06907
JST JPMJMS2295

Title: Noradrenaline Regulates Behavioral State Transitions under a Probabilistic Decision-Making Task in Monkeys

Authors: *T. BANNO[1], Y. HORI[1], Y. NAGAI[1], Y. HORI[1], S. NAKAMURA[2], K.-I. TSUTSUI[2], T. MINAMIMOTO[1];
[1]Advanced Neuroimaging Ctr., Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan; [2]Lab. of Systems Neurosci., Tohoku Univ. Grad Schl Life Sci., Sendai, Japan

Abstract: Neurocomputational models of decision-making infer choice components, such as sensory sensitivity and decision bias, from the behavior of well-trained animals by assuming stable performance throughout a session. However, behavioral performance often fluctuates even in expert animals. While such fluctuations are typically interpreted as lapses in attention or motivation, a recent study has suggested that they may instead reflect adaptive switching among distinct behavioral strategies. Here, we hypothesized that noradrenaline (NA), a neuromodulator associated with arousal and behavioral flexibility, plays a key role in regulating such dynamics, and investigated the role of NA in strategy switching under a task with uncertain behavioral outcomes. Two Monkeys performed a Go/No-Go licking task in which visual cues indicated probabilistic delivery of appetitive juice or aversive saline (five visual cues indicated 0/100, 25/75, 50/50, 75/25, or 100/0 percent chance of juice/saline delivery). Applying a Generalized Linear Model Hidden Markov Model (GLM-HMM) analysis, we found that the monkeys spontaneously switched among three states: an early exploration state for learning cue-outcome contingencies switched later into an exploitative state optimizing reward while avoiding saline, with an intermittent disengaged state characterized by licking suppression. Pharmacological manipulations further showed that increasing NA by reboxetine (a selective NA reuptake inhibitor; 0.4 mg, im) prolonged the exploration state, whereas decreasing NA by clonidine (an alpha 2 receptor agonist; 10-20 ug/kg, im) increased the duration of the disengaged state. Together, these results demonstrate that noradrenergic modulation governs transitions between exploration, exploitation and disengaged states, revealing a mechanistic substrate for flexible decision-making under uncertainty.

Disclosures: T. Banno: None. **Y. Hori:** None. **Y. Nagai:** None. **Y. Hori:** None. **S. Nakamura:** None. **K. Tsutsui:** None. **T. Minamimoto:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.09/KK39

Topic: I.03. Decision Making

Support: NIH R01AA031609

Title: Anterior cingulate cortex encodes cue uncertainty that asymmetrically modulates learning from wins and losses

Authors: *S. KALHAN[1,2], S. BROOKE[3], Y. CHENG[2,5], K. IBRAHIM DIT NASRALLAH[4], I. LEE[4], P. H. JANAK[2,5,3];
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Abstract: The anterior cingulate cortex (ACC) is thought represent uncertainty levels to adjust how much is learnt from feedback. Yet, learning rates also depend on feedback valence where positive and negative outcomes are known to engage distinct subcortical dopamine-mediated learning processes. Whether ACC representations of uncertainty also contribute to the asymmetric weighting of positive and negative feedback remains to be tested. Here, we used Neuropixels 2.0 probes inserted in ACC to record neural activity while Long-Evans rats performed a cue uncertainty learning paradigm. On each trial, rats were presented with one of three distinct auditory cues. Two of these cues were informative (i.e., they instructed the rat which lever, left or right, to press to obtain sucrose reward), and the third cue was uninformative (i.e., 50% reward probability for either lever press). In a subset of sessions, informative cues predicted outcomes probabilistically, yielding trials with surprising wins and losses (correct presses that lost, incorrect presses that won). We found that rats (n=19 rats; 11M, 8F) had reduced feedback sensitivity when outcomes were predicted by uninformative cues, based on lower learning rates (using a Rescorla-Wagner model) and higher stay probabilities from these cues. Importantly, rats were equally likely to stay following wins and losses under uninformative cues, but under informative cues wins were weighted more than losses (higher probability of win-stay v. lose-shift). This asymmetrical learning effect extended to surprising trials where surprising wins impacted behavior more than surprising losses. Neurons in ACC (n = 218 single units across 2 rats) encoded both cue uncertainty and outcome valence. During the cue period, neurons were cue-selective, with 33% preferring informative cues and 29% uninformative cues (Wilcoxon signed-rank, FDR-corrected, $p<0.05$) confirming sensitivity to uncertainty. At outcome delivery, a Poisson GLM revealed 25.6% of neurons showed a main effect of cue uncertainty and 53.7% a main effect of outcome valence ($p<0.05$, FDR-corrected). Importantly, a subpopulation of neurons (9.8%) showed a significant cue uncertainty × outcome valence interaction, providing evidence that ACC may compute signals relevant for scaling wins and losses. Together, these results show that cue uncertainty modulates the asymmetric weighting of wins and losses, and identify the ACC as a candidate substrate where uncertainty and valence are jointly encoded. These findings suggest a cortical contribution to asymmetrical feedback learning, beyond the known subcortical dopamine-mediated processes.

Disclosures: S. Kalhan: None. **S. Brooke:** None. **Y. Cheng:** None. **K. Ibrahim Dit Nasrallah:** None. **I. Lee:** None. **P.H. Janak:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.10/KK40

Topic: I.03. Decision Making

Title: GABA-B receptor signaling in the superior colliculus-ventral tegmental area pathway regulates visual cue-guided reversal learning in rats

Authors: *A. M. WAGHADE[1], S. A. GAIKWAD[1], A. P. GIRI[1], S. N. AWATHALE[2], N. K. SUBHEDAR[3], D. M. KOKARE[1];
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Abstract: The superficial grey layer (SuG) of the superior colliculus (SC) serves as a key hub for processing visual signals and directing orienting and approach behaviors. GABA-B receptors, which are highly expressed in the SuG, play a pivotal role in regulating visual response dynamics. Notably, GABAergic neurons in the SuG receive direct retinal inputs and provide monosynaptic inhibition on dopamine (DA) neurons in the ventral tegmental area (VTA), a central node in motivated behavior and reversal learning/cognitive flexibility. In this study, we uncover a novel mechanism of GABA-B receptor signaling in the SuG-VTA circuit in visual cue-guided reversal learning. Using a rat model, we showed that pharmacological activation of GABA-B receptors in the SuG with baclofen enhanced active lever pressing in reversal task, while antagonism with phaclofen impairs these behaviors. Importantly, intra-SuG baclofen administration partially reversed the cognitive deficits induced by MK801, a compound known to disrupt reversal learning. At the molecular and cellular level, improved reversal learning correlated with upregulated GAD67 expression, elevated GABA/glutamate levels, and increased dendritic arborisation and spine density in SuG, as demonstrated by qRT-PCR, immunohistochemistry, HPTLC, and Golgi-Cox staining. Furthermore, intra-VTA baclofen microinjection in reversal-trained rats reduced lever pressing but increased DA turnover in the nucleus accumbens shell, as measured by microdialysis HPLC-ECD. Collectively, these results reveal that GABA-B receptor-mediated inhibition within the SuG-VTA pathway acts as a critical regulator of reversal learning/cognitive flexibility by integrating sensory input with downstream dopaminergic signaling. This reveals that SuG GABA-B signaling is crucial for adaptive motivated behaviors and provides new understanding of the neural basis of cognitive flexibility.

Disclosures: A.M. Waghade: None. **S.A. Gaikwad:** None. **A.P. Giri:** None. **S.N. Awathale:** None. **N.K. Subhedar:** None. **D.M. Kokare:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.11/KK41

Topic: I.03. Decision Making

Support: NIAAA Grant R01AA024845
NIAAA Grant F32AA032136

Title: Alcohol-induced hyperexcitability of claustrocortical circuitry impairs flexible behavior.

Authors: *A. B. WULFF, S. H. SHEATS, J. A. WASHINGTON, B. N. MATHUR;
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Abstract: Cognitive control dysfunction is a key component of alcohol use disorder that fosters inflexible alcohol consumption. The claustrum, a key cognitive control nucleus, receives strong input from the anterior cingulate cortex (ACC). Recently, in mice, we found that chronic alcohol exposure enhances the excitatory drive of claustrum projection neurons by the ACC. Whether this effect is specific to claustrum projection neuron subpopulations based on their output targets is unknown. We found that chronic alcohol exposure enhanced excitatory drive of the ACC onto claustrum neurons projecting to the parietal association cortex (PtA) but not the prelimbic prefrontal cortex (PrL), cortical areas homologous to cognitive network nodes. When mimicking the alcohol-induced hyperactive state of the claustrum-PtA circuit chemogenetically, mice exhibited impaired flexible reward seeking during a reversal learning task and continued to drink alcohol even when adulterated with high concentrations of the bitter tastant quinine. In contrast, chemogenetic inhibition of this circuit decreased quinine-adulterated alcohol consumption. Together, these data suggest that chronic alcohol exposure increases excitability of the cingulo-claustro-PtA circuit resulting in impaired cognitive control of flexible alcohol consumption.

Disclosures: A.B. Wulff: None. **S.H. Sheats:** None. **J.A. Washington:** None. **B.N. Mathur:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.12/KK42

Topic: I.03. Decision Making

Support: NINDS R01NS121913
NIMH DP2MH122404
NIH T32NS126122-02

Title: Dissociable parietal subnetworks for stability and flexibility support adaptive decisions

Authors: *A. BANDI[1], C. A. RUNYAN[2];
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Abstract: Adaptive behavior requires representing the same decision across changing sensory contexts, yet how cortical circuits reconcile the stability this demands with the flexibility to exploit context-specific cues is unclear. To study cortical network properties supporting adaptive decisions, we trained mice to perform a virtual-reality T-maze task in explicitly different visual and auditory contexts and imaged the activity of more than 60,000 posterior parietal cortex (PPC) neurons in layer 2/3. Cross-context decoding revealed that decision information partially generalized across contexts, indicating that context-invariant and context-dependent decision codes coexist in the PPC population. To characterize the task-related features that explain activity in these populations, we fit an encoding model to predict neuronal activity across contexts and scored each neuron's context preference. The encoding model revealed that cross-context generalization was carried exclusively by context-invariant neurons. Functional coupling to the surrounding population declined with context dependence: context-invariant neurons coupled preferentially to one another and formed a backbone for computation that is tightly embedded to the local population, while context-dependent neurons formed a sparsely coupled periphery. We then sought to test this network architecture by training the same mice to make decisions in two novel, multisensory contexts. In the first multisensory context, mice were presented with congruent audio-visual cues that offered redundant sensory information. Behavior improved in this context and selectively sharpened the encoding of only the context-dependent neurons. In the second multisensory context, mice were presented with incongruent audio-visual evidence that offered conflicting choices. Mice learned to resolve this conflict by implicitly inferring the relevant modality and adapted to covert context switches. The incongruent multisensory context also preferentially reorganized context-dependent neurons. Through both behavioral manipulations the coupled invariant backbone was conserved and largely unmodulated. PPC thus reconciles stability and flexibility through separable populations with unique network coupling properties. A coupled, context-invariant core anchors a generalizable decision, and a context-dependent periphery is reconfigured based on contextual demand. These results show that coexisting subnetworks support adaptive decisions and identify coupling as a representational axis for context within a neuronal population.

Disclosures: A. Bandi: None. **C.A. Runyan:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.13/KK43

Topic: I.03. Decision Making

Support: MH 119391

Title: The Medial Prefrontal Cortex Supports Adaptive Strategy Switching

Authors: *M.-R. A. MBAH[1], B. ACKMANN[2], S. J. MIZUMORI[3];
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Abstract: A critical process for survival involves changing our behavior in response to changing environmental contingencies, a process known as behavioral flexibility, which is mediated by the medial prefrontal cortex (mPFC). Neural recordings from the mPFC suggest its involvement in working memory, which aids in choice/action selection and in learning the structure, rules and strategies in a given task. However, the precise nature of the mPFC's involvement in strategy switching between learned behavioral strategies in ways that reflect changing task demands remain under explored. Furthermore, we aimed to decouple flexibility from adaptability in order to understand the contexts within which mPFC-guided flexibility is adaptive. To address these questions, we transiently inactivated the mPFC of 10 Long Evans rats using muscimol, a GABA-A receptor agonist, and analyzed their performance on a recently developed maze-based strategy switching task with uncued switches. Rats learned 2 strategies that led to sucrose rewards - place (returning to the same reward arm) and alternation (alternating between reward arms) strategies. The mPFC's involvement in learning the strategies on this task was confirmed through our observation of a significant increase in the number of trials it took rats in the inactivation group to learn the target strategy within a block, along with an increase in the number of trials it took to complete a block. We also observed that about 5 trials after an uncued switch, mPFC inactivation significantly impaired choice accuracy, alongside a significant increase in the number of errors made throughout the session. These results indicate the mPFC's role in supporting switching to the target strategy after an unexpected switch in a timely manner. Our results also revealed that mPFC inactivation led to an increase in perseverative behavior seen through a decrease in the use of the lose-shift strategy. Interestingly, after a perseverative error, there was a significant increase in flexibility (change in using the task strategies) in the muscimol group, but a significant decrease in using the target strategy after this error, indicating that this flexibility was not adaptive. These results demonstrates that the functional contribution of the mPFC in strategy switching may be to incorporate information about errors, in particular perseverative errors, in order to guide adaptive behavioral change.

Disclosures: M.A. Mbah: None. **B. Ackmann:** None. **S.J. Mizumori:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.14/KK44

Topic: I.03. Decision Making

Title: A prefrontal neural pathway for adaptive sleep interruption

Authors: *H. ZHU[1], R. WIMMER[3], N. H. LAM[4], N. REDDER[1], J. SCOTT[1], Y. WANG[2], M. A. PENZO[5], M. HALASSA[1];
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Abstract: Sleep is an evolutionarily conserved behavior, essential for functions such as energy homeostasis, toxic waste removal, and systems-level memory consolidation. While significant progress has been made in understanding these ancillary functions, the mechanisms by which sleep itself is rapidly modulated in response to environmental contingencies remain poorly understood. Specifically, the mechanisms trading off vigilance with restorative processes are an open area of investigation: what are the neural mechanisms that allow the brain to selectively wake up to pursue rewarding opportunities or avoid potential harm? It is widely known that selective sensorimotor processing is preserved during sleep, where a mother would awaken to the crying of her own child or a healthcare provider wake up to the sound of their specific pager. Both associative and contextual factors contribute to this process: as in the previous examples, individuals are more likely to awaken when their name is called (an associative factor), and fireworks on New Year's Eve are less arousing than at other times, highlighting the importance of context. Neuroimaging has identified involvement of the amygdala, thalamus and prefrontal cortex (PFC) in such settings, but the precise mechanisms remain elusive due to challenges in probing these circuits in the human brain. To address these challenges, we established a mouse model that enables mechanistic investigation of adaptive sleep interruption. Using an adapted shuttle-box assay to examine avoidance and reward-seeking behaviors, we discover that auditory conditioning results in selective sleep interruption that is causally dependent on the amygdala. Importantly, our findings indicate that this associative sleep interruption generalizes across both appetitive and aversive conditioning paradigms, suggesting that this process reflects a broader mechanism for adaptive behavioral engagement rather than a specifically defensive or stress-related response. Electrophysiological recordings in task-performing mice reveal amygdala circuit reorganization following associative conditioning. By examining sleep interruption in different behavioral arenas, we find that mice also show contextual behavioral specificity, and that this process engages prefrontal cortex. Prefrontal inhibition reinstates sleep interruption in safe environments, along with the underlying amygdala transformation supporting it. Overall, our work shows a prefrontal to amygdala pathway for adaptive sleep interruption, extending the notion of top-down executive control to decision making during sleep.

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Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.15/KK45

Topic: I.03. Decision Making

Support: CHDI Foundation Project A-18015

Title: HTT targeting divalent siRNA treatment ameliorates lack of cognitive flexibility in zQ175 Huntington's disease mouse model

Authors: *F. MORGADO[1], I. GILDISH[1], C. F. CARDOZO HERNANDEZ[1], E. MCDONNELL[2], J. F. CHEER[1];
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Abstract: Huntington's disease (HD) is a progressive neurodegenerative disease caused by the expansion of a CAG repeat in the huntingtin gene (HTT). Despite more than three decades since the identification of the HTT gene, there is yet no cure for HD, with treatment strategies restricted to symptomatic control. Symptom presentation initiates with difficulties in executive functioning, anxiety, depression and minor changes in coordination (prodromal stage), progressing towards chorea and more severe motor dysfunctions in later stages. With the emergence of gene therapy, multiple strategies are currently under pre/clinical trials to restrict or prevent the expression of the mutant HTT. Here, we employ an intracerebroventricular divalent siRNA (di-siRNA) targeting HTT for sustained gene downregulation in the zQ175 HD mouse model and assess its effects over cognitive deficits, characteristic of this disease. zQ175 mice were trained on a probabilistic reversal learning paradigm to evaluate how HD impairs cognitive flexibility and decision-making under uncertainty. Dopaminergic (DA) release dynamics in the Nucleus Accumbens was quantified through fiber photometry to observe how HD's striatal degeneration impairs the mesolimbic pathway. Wild-type (WT) mice obtained higher number of rewards than zQ175 during the task. This occurred due to the elevated number of trials where zQ175 mice failed to press a lever during the availability window (omitted trial) and for the impairment in the discrimination of the high rewarding lever as shown by a smaller accuracy when compared to WT mice. Interestingly, zQ175 mice needed more trials to revert contingencies, took longer to make a choice between both levers and increased perseverative errors. Treatment with di-siRNA restored to some extend this flexibility by increasing the probability of zQ175 mice to shift towards a high rewarding lever after receiving no reward in the low probability one. Accumbal DA dynamics suggests that zQ175 have decreased release at cue-tone onset and prior to reward delivery in rewarded presses. For unrewarded presses, the di-siRNA treatment was able to partially reverse the smaller DA release of zQ175 in the expectation of a reward. Our findings indicate that zQ175 mice lack flexibility due to impaired reward prediction error encoding. HTT targeting di-siRNA was able to ameliorate this to some extent. These results align to what has been observed in HD patients who show impaired probabilistic discrimination and increased perseverative responding and provide evidence that HTT targeting therapies may be beneficial for preventing or restoring the cognitive decline that afflicts HD patients.

Disclosures: F. Morgado: None. **I. Gildish:** None. **C.F. Cardozo Hernandez:** None. **E. McDonnell:** None. **J.F. Cheer:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.16/KK46

Topic: I.03. Decision Making

Support: NIH R01 R01MH122844

Title: Acute Vaporized Cannabis Exposure Alters Decision-Making and Dopamine Signaling in the Nucleus Accumbens Shell During a Dynamic Foraging Task.

Authors: *A. M. AMAYA, Z. FISHER, M. M. MUIR, R. J. MCLAUGHLIN;
Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Acute Vaporized Cannabis Exposure Alters Decision-Making and Dopamine Signaling in the Nucleus Accumbens Shell During a Dynamic Foraging Task Amaya, A.M., Fisher, Z.D.G., Muir, M., McLaughlin, R.J.Cannabis use is associated with disruptions in reward-based decision-making, yet the neural mechanisms underlying these disruptions remain poorly understood. The nucleus accumbens shell (NAcSh) critically encodes action-outcome associations via dopaminergic signaling during reinforcement learning. However, the extent to which cannabis exposure modulates NAcSh dopamine signaling during active decision-making has not been directly tested. Thus, we addressed this knowledge gap by training rats on an operant-based dynamic foraging task (i.e., probabilistic reversal bandit task) that leverages optimal foraging theory and reinforcement learning to create a dynamic environment in which subjects must continuously learn and adjust behavioral strategies to maximize reward. Prior to training, rats received unilateral injections of the dopamine biosensor dLight1.3b (pAAV-CAG-dLight1.3b) into the NAcSh and were given at least one week to recover. Upon establishing a stable baseline of responding in the dynamic foraging task, rats were habituated to non-contingent vapor delivery for 3 days prior to the first test day. On the first test day, rats were counterbalanced to receive acute exposure to cannabis (150 mg/ml whole plant extract containing 63.9% THC) or vehicle (VEH; PEG-400) vapor at a frequency of one 3-s puff every 2 min for 60 min. On the following day, rats exposed to cannabis vapor were exposed to VEH and vice versa for within-subject comparisons. Dopamine recordings in the NAcSh were conducted using *in vivo* fiber photometry and transients were time-locked to relevant decision-making events for time-resolved analysis of dopamine dynamics. Behavioral data indicate greater NAcSh dopamine signaling on lower-probability rewarded trials and more signaling uniformity between choice outcomes during late- vs. early-block epochs. Notably, acute vaporized cannabis exposure prior to decision-making significantly altered dopamine signaling during all outcomes of the task. Additionally, we observed decreased post-switch adaptation, reduced sensitivity to reward contingencies, increased perseverative errors, decreased choice bias and more exploitative

decision-making compared to VEH exposure. Overall, our results suggest that acute cannabis exposure alters dopamine recruitment in the NAcSh in a manner consistent with disrupted explore-exploit decision-making.

Disclosures: A.M. Amaya: None. **Z. Fisher:** None. **M.M. Muir:** None. **R.J. McLaughlin:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.17/KK47

Topic: I.03. Decision Making

Support: NIH NIA R25AG076396
AARGD-22-972117

Title: Quantification of cocaine-induced psychomotor plasticity in elder individuals using automated behavioral analysis

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

Abstract: Experience-dependent neural plasticity can drive both adaptive and maladaptive behavioral shifts, such as those observed in addiction and cognitive aging. Addiction represents a profound failure of the decision-making system, where the brain becomes hyperreactive to drug-related cues and loses its capacity to weigh long-term consequences against immediate rewards. Circadian clock genes are increasingly recognized as key regulators of neural plasticity and behaviors beyond simple timekeeping, both of which are also significantly impacted by aging. However, the exact neural mechanisms governing the transition between different drug-induced behavior states such as hyperactivity, hypoactivity, and sedation, remain poorly understood. This study investigates how the circadian clock neuronal network and the core circadian genes, clock and period, regulate cocaine-related psychomotor behaviors. Furthermore, by leveraging our Drosophila model, we investigate how these drug-induced behavioral transitions and their underlying circuit mechanisms alter during the natural aging process.Utilizing the genetically tractable model Drosophila melanogaster, we evaluated the progressive changes of locomotor responses to repeated drug exposure. To ensure precise control over the exact drug dose administered, wild-type flies were temporarily immobilized within a modified pipette tip and manually administered increasing dosages of cocaine via a micropipette. Following administration, locomotor behavior was recorded in an open-field arena. Video tracking data was subsequently processed using a Python-based, custom-made automated tracking pipeline (y-flybatch application) to precisely encode Δx, Δy coordinates and quantify instant speed as the primary metric for behavioral response to cocaine. Further computational analysis enabled us to define a dose-dependent profile, where high doses exceeding 100 nanograms of cocaine

consistently induced a complete locomotor suppression. Below this 100 nanogram threshold, decreasing dosages uncovered a dual effect in which intermediate doses produced hypoactivity, whereas a lower, minimum threshold dose elicited hyperactivity. Furthermore, repeated administration synergistically amplifies these responses.The ability of modeling these behaviors in Drosophila is instrumental for our long-term goal of understanding the molecular and cellular mechanisms that govern decision making and maladaptive behaviors. We are particularly interested in the role that cocaine sensitization plays in drug seeking behaviors and how the circadian clock regulates them.

Disclosures: A. Calavia: None. **I. Nieves:** None. **A. Martin-Peña:** None.

Poster

PSTR330: Decision Making: Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR330.18/KK48

Topic: I.03. Decision Making

Support: HHMI

Title: Engagement of Anterior Thalamic Nuclei in unguided sequence learning settings

Authors: *E. KULESHOVA[1], D. G. TERVO[1], A. Y. KARPOVA[2];
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Abstract: Recent studies in stimulus-guided learning settings probing the role of anterior thalamic nuclei in non-spatial cognition have provided two seemingly unrelated accounts: in selection of memories for consolidation and in the processing of sequential information. These two functions may be different sides of the same coin in unguided, open-ended learning settings where sparse rewards must be attributed to a specific, but difficult to discover, sequence of events or actions. Indeed, ATN nuclei provide strong glutamatergic projections to the medial frontal cortex which we have recently implicated in unguided discovery of sequential explanations in open ended settings in rats. We now build on this behavioral framework to probe the neural activity patterns in ATN in relation to task contingencies, and in comparison with patterns in the medial frontal cortex.

Disclosures: E. Kuleshova: None. **D.G. Tervo:** None. **A.Y. Karpova:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.01/KK49

Topic: I.04. Executive Functions

Support: NIH Grant R01MH129042

Title: Flexible control of intrusive thoughts depends on multiple inhibitory mechanisms

Authors: *C. N. JERINIC-BRODEUR[1], Z. BRETTON[2], M. ROWLANDS[3], L. SAHAKYAN[4], M. C. ANDERSON[3], J. A. LEWIS-PEACOCK[1];
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Abstract: The ability to control unwanted memories is a core feature of human cognition that supports adaptive behavior. Inhibitory control can be exerted over representations in long-term memory (LTM; retrieval stopping) and working memory (WM; maintenance suppression) to modulate their accessibility. When retrieval stopping fails, unwanted information intrudes into awareness, creating a demand to reestablish control. Prior accounts have proposed that individuals recover from intrusions by reengaging the same inhibitory process that targets retrieval—a domain-general mechanism shared with action stopping. However, once an intrusion has occurred, additional processes may be needed to purge the unwanted content from awareness. We hypothesized that maintenance suppression is a reactive process, uniquely engaged to counteract intrusions that escape retrieval stopping. Although maintenance suppression and retrieval stopping share overlapping neural mechanisms, they may reflect fundamentally distinct control operations. To test this, we developed a novel fMRI paradigm integrating the Think/No-Think task, which engages retrieval stopping from LTM, with a directed removal task, which engages maintenance suppression from WM. Participants (N = 51) learned arbitrary cue-target image pairs before completing alternating WM and LTM control blocks during fMRI scanning. In WM blocks, participants viewed a target image for 3 s and were instructed to either maintain or suppress it for 10 s. In LTM blocks, participants viewed cue images for 3 s and were instructed to retrieve (Think) or stop retrieval (No-Think) of the associated target for 10 s. Participants reported if the target image intruded into awareness at the end of each trial. fMRI pattern classification revealed a double dissociation within the prefrontal cortex (PFC). Each control strategy produced a distinct, reliably decoded pattern of PFC activity. Yet both strategies recruited overlapping subregions, suggesting a partially shared neural substrate for WM and LTM control. Critically, when retrieval stopping failed and intrusions occurred on No-Think trials, fMRI decoding revealed reactive engagement of maintenance suppression to purge unwanted content from awareness. Together, these findings challenge unitary accounts of inhibitory control and support a revised model in which distinct, partially overlapping mechanisms are selectively engaged to prevent unwanted memories from occupying the focus of attention. Successful memory control depends not on retrieval stopping alone, but on the reactive recruitment of maintenance suppression to resolve its failures.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

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Program #/Poster #: PSTR331.02/KK50

Topic: I.04. Executive Functions

Support: NIH Grant 1R21MH127009-01A
DARPA Cooperate Agreement Number W911NF-14-2-0045

Title: Frontotemporal Network Dynamics Supporting Cognitive Control in Humans are Enhanced by Intracranial Electrical Capsular Stimulation

Authors: *A. SHEKARA[1], A. ROSS[2], A. C. PAULK[4], A. S. WIDGE[5], S. S. CASH[4], P. K. SHEAR[3], I. BASU[2];
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Abstract: Cognitive control, or flexible adaptation in the face of conflicting options, is essential for maintaining goal-directed behavior and frequently compromised in neuropsychiatric disorders. Cognitive conflict evokes theta (4-8Hz) and high-frequency (70-110Hz) activity in dorsolateral and dorsomedial prefrontal cortex (dlPFC and dmPFC) that facilitate effective control, and distributed oscillations across orbitofrontal cortex (OFC), lateral temporal lobe (LTL), amygdala, and hippocampus. However, the role of these temporo-limbic oscillations in cognitive control remains unclear. Here, we used stereotactic EEG (sEEG) recordings during a cognitive control task and direct electrical stimulation to examine frontotemporal network dynamics during successful conflict resolution.
We obtained sEEG recordings in frontotemporal regions of 20 human participants with intractable epilepsy performing a multi-source interference task (MSIT) as part of a previous study. A subset of patients (n=6) performed a second MSIT session during 130Hz capsular stimulation. Functional connectivity in the theta band was measured using phase-locking value (PLV). Generalized linear mixed-effects models and nonparametric cluster-based permutation tests were used to examine effects of conflict (low, high) and stimulation (OFF, ON) on reaction times and frontotemporal theta and high-gamma spectral power, and effects of conflict on theta PLV across frontotemporal networks.
In non-stimulated sessions, conflict increased reaction times and enhanced pre-response theta power in dmPFC, LTL, and hippocampus. High-gamma power was increased across PFC and reduced in temporo-limbic structures during conflict. Single-trial response times were negatively correlated with theta power in dlPFC and hippocampus and positively correlated with high-gamma power in dorsal and ventral PFC. Conflict enhanced theta PLV between dlPFC-dmFPC, dlPFC-HIP, and LTL-HIP. Capsular stimulation reduced reaction times during the MSIT for high conflict but not low conflict trials, while enhancing conflict-related theta power in dlPFC, dmPFC and LTL.
Conflict enhanced frontotemporal theta oscillations and local population activity in prefrontal cortex while suppressing local activity in temporo-limbic regions. Our findings provide initial evidence for frontotemporal theta networks supporting conflict resolution. Biophysical modeling

of network dynamics during electrical stimulation can further elucidate frontotemporal mechanisms supporting cognitive control, and inform therapeutic strategies for restoring cognitive function in neuropsychiatric disorders.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.03/KK51

Topic: I.04. Executive Functions

Support: Albstein Research Scholarship
NIMH: R01MH137085

Title: Neural Dynamics of Self-Control: Pre-Choice EEG Signals Predict Yielding to Temptation

Authors: W. LEONG, *V. STUPHORN;
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Abstract: Self-control, the capacity to resist immediate impulses in favor of long-term goals, is fundamental to adaptive human behavior, yet its neural dynamics remain unclear. A key limitation of prior research is that commonly used tasks conflate self-control with value evaluation, making it difficult to isolate the construct of interest. Here, we introduce a novel dynamometer-based paradigm in which participants choose between a high-effort, larger-later (L) reward and a low-effort, smaller-sooner (S) reward initially. Crucially, some trials introduce a temptation to switch, allowing participants to either maintain their original commitment or give in to the alternative option. We categorized behavior into six primary trial types: in no-temptation trials, participants simply chose the L or S option. In temptation trials, they either maintained their initial commitment (LL or SS) or switched to the alternative reward (LS or SL). Twenty-six participants completed the task while a 32-channel electroencephalogram (EEG) was recorded. In temptation trials, the choice function based on final choices was significantly shifted towards a preference for less delayed options relative to the one for initial choices. This was produced by substantially more LS than SL switches. EEG activity predicted yielding (LS) or resisting temptation (LL) well before the initial choice. First, a late positive potential (LPP) differentiated LL from LS trials during the pre-choice (692-796ms post-option presentation), localized to the left posterior cingulate visual area and somatosensory regions. This greater positivity in LS trials might reflect heightened motivational conflict and increased attentional engagement with choice alternatives prior to yielding. No significant difference in N1 amplitude was observed between LL and LS trials, suggesting that early attentional filtering does not reliably distinguish self-control outcomes within this paradigm. Second, time-resolved

multivariate decoding revealed that EEG patterns reliably discriminated LL from LS outcomes and peaked 304-348ms post-stimulus onset, driven by distributed frontal and centroparietal networks rather than any focal electrode. In addition, the pre-release activity predicts the final choice of the trial, reflecting reward anticipation scaled by reward magnitude at the motor execution period. Together, these findings support a neural mechanism of self-control that is established before the choice, with proactive neural states during deliberation shaping self-control success and failure.

Disclosures: W. Leong: None. **V. Stuphorn:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.04/KK52

Topic: I.04. Executive Functions

Support: R01MH137085

Title: The role of macaque orbitofrontal and anterior insular cortex in self-control

Authors: *K. LEE[1,2], V. STUPHORN[1,3];
[2]Dept. of Psychological and Brain Sci., [3]Dept. of Neurosci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Exercising self-control under temptation is crucial for pursuing long-term goals. However, the neural basis of self-control remains elusive, in part because self-control is often confounded with value-based choice. Our self-control task addresses this issue by identifying high and low self-control states while keeping the value-based choice constant. In this self-control task, the monkey made a saccade to indicate their choice between a smaller, sooner (S) and a larger, later (L) reward. On a rare and randomly interleaved subset of trials, termed temptation trials, the unchosen option remained available, requiring self-control to resist switching from the more costly, but optimal, L option to the suboptimal S option. Critically, in this situation of heightened need for self-control, the monkey was sometimes able to resist temptation (maintained L option) and sometimes failed to do so (switched to S option). Temptation trials provide therefore a clear behavioral marker for the level of self-control exerted on a trial-by-trial basis, independent of the initial value-based choice (the initial L choice). Using this task, previous work in our lab investigated the frontal executive control system and identified a clear neural signature of proactive self-control, predictive of whether monkeys would resist or give in to temptation after initially choosing the more prudent option. Here, we extend this work by investigating the role of the value-encoding system in self-control. We distinguish between two mechanistic hypotheses to explain the trial-by-trial variability in self-control strength. First, signals related to valuation (both costs and/or benefits) and internal-state processing could determine the strength of proactive control mechanisms. Second, proactive

control mechanisms could determine the value of options and thus bias choice. To test these hypotheses, we recorded from neurons in the orbitofrontal and anterior insular cortex, regions implicated in value-based decision-making, contextual valuation, and interoception, while a macaque monkey performed the self-control task. We will present preliminary neuronal results examining the role of value and internal-state signals in shaping the momentary level of proactive self-control, that enables the selection and maintenance of prudent long-term goals.

Disclosures: K. Lee: None. **V. Stuphorn:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.05/KK53

Topic: I.04. Executive Functions

Support: NIH Grant R01MH137085

Title: Using Poisson Generalized Linear Models to Distinguish Proactive and Reactive Control in Behavioral Inhibition

Authors: *M. INCEBOZ[1], J. ELSEY[2], V. STUPHORN[3];
[1]Neurosci., [2]The Zanvyl Krieger Mind/Brain Inst., [3]Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Behavioral control is a key component of action selection during decision-making. Motor control pathways include Supplementary Eye Fields (SEF) and Dorsolateral Prefrontal Cortex (DLPFC) that are involved in saccade inhibition and cancel eye movements planned by the Frontal Eye Fields (FEF). Similarly, motivational control can allow for the suppression of temptation to give up in effortful tasks and exert self-control to achieve a preferred outcome. Given its clinical relevance in many psychopathologies, including disorders of excessive aggression, addiction, or eating disorders, behavioral control and the lack thereof can be studied in animal models to uncover its underlying mechanisms.Two main mechanisms of behavioral control are proactive and reactive control. Proactive control is employed in anticipation of task requirements, whereas reactive control occurs in reaction to sudden changes. We investigated behavioral control in macaque monkeys using the stop signal and the self-control task, representing motor and motivational control, respectively. In the stop signal task, monkeys made a saccade to a peripheral target. On a subset of trials, a visual stop signal was presented after a variable stop-signal delay, requiring the inhibition of the ongoing saccade preparation. The self-control task is an intertemporal choice task, in which monkeys chose between rewards of different magnitudes and delays. On a subset of trials, termed temptation trials, the unchosen option remained available, requiring self-control to resist switching from the more costly, but optimal, L option to the suboptimal S option. The monkey was sometimes able to resist temptation and sometimes failed to do so. Temptation trials provide therefore a clear behavioral

marker for the level of self-control exerted on a trial-by-trial basisWe conducted concurrent acute neural recordings from frontal cortical areas including FEF, SEF, DLPFC, and Ventrolateral Prefrontal cortex (VLPFC). Using Poisson generalized linear models, we dissociated the neural response to distinct events, such as target appearance and saccades, as well as to proactive and reactive control. This encoding model allowed us to determine the number and relative strength with which individual neurons and populations in different areas represented proactive versus reactive control signals. A decoding model allowed us to assess how well success or failure of control could be predicted based on the reconstruction of neural responses from the control event kernel weights.

Disclosures: M. Inceboz: None. **J. Elsey:** None. **V. Stuphorn:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.06/KK54

Topic: I.04. Executive Functions

Title: Examining the Role of Retrieval Suppression in Fear Extinction

Authors: *D. SINGH[1], J. PACIOS[3], M. K. ASTHANA[1,2];
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Abstract: Exposure therapy, analogous to extinction learning, is a prominent therapeutic technique utilized to treat maladaptive fear responses. However, its outcome is often unsuccessful. Impaired inhibitory control has been proposed as a major factor underlying unsuccessful fear extinction. Therefore, enhancing these underlying inhibitory mechanisms might facilitate extinction learning. In the retrieval-suppression model of fear extinction, retrieval stopping is an essential component of extinction learning. However, the role of retrieval suppression in enhancing extinction learning has been underexplored. Therefore, the present study aims to examine how activation of the underlying retrieval-stopping inhibitory mechanisms during extinction could modulate the conditioned fear responses and their persistence utilizing a three-day differential auditory fear conditioning paradigm. The experiment included four phases: a habituation and acquisition phase on day 1, extinction on day 2, and an extinction recall test on day 3. The outcome measures included arousal, valence, and expectancy ratings obtained across phases. Twenty-four participants were randomly divided into two groups: Standard Extinction (SE) and Standard Extinction with No Think instruction (SE-NT). The SE-NT group was instructed to consciously suppress the associated consequences of the stimuli presented within a red-coloured border. A rmANOVA with stimuli and phase as within-subject factors and group as a between-subject factor revealed significant stimulus × phase interactions for arousal ($F(3, 66) = 15.78$, $p < .001$, $\eta p^2 = .42$), valance ($F(3, 66) = 9.65$, $p < .001$, $\eta p^2 = .31$) and expectancy ($F(2, 44) = 9.75$, $p < .001$, $\eta p^2 = .35$). In both groups, CS+ elicited higher

arousal, negative valence, and higher expectancy ratings during the acquisition phase. Across phases, these responses decreased from the acquisition to the extinction phase and were maintained during extinction recall, indicating successful conditioning and extinction learning. However, no significant group differences were observed. The present ongoing study did not indicate an effect of retrieval suppression on extinction learning.

Disclosures: D. Singh: None. **J. Pacios:** None. **M.K. Asthana:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

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Program #/Poster #: PSTR331.07/KK55

Topic: I.04. Executive Functions

Support: This study was funded by internal startup funds awarded to Kristen R. Hoskinson.

Title: Examining the association between hippocampal volume and NIH Toolbox performance in youth

Authors: *F. ONTIVEROS[1], W. I. MATTSON[1], K. R. HOSKINSON[1,2], K. VANNATTA[1,2], C. GERHARDT[1], E. E. NELSON[1,2];
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Abstract: The hippocampus is a key neural structure that supports human cognition, and hippocampal volume has been linked with specific neurocognitive domains such as working and relational memory and processing speed. However, much of this research comes from adult and aging populations and the extent to which these findings extend to children and adolescents still undergoing active neurodevelopment remains less clear. This project aims to describe the relationship between hippocampal volume and performance across different domains of neurocognitive functioning assessed with the NIH Toolbox Cognition Battery (NIHTB-CB) in youth. This battery, widely used in neuropsychological testing, includes subtests tapping a variety of cognitive domains. A group of 107 typically developing children and adolescents, 8-21 years old (M_{age}=13.56yr, Male=40.2%), underwent MRI in a 3T Siemens Prisma scanner, which included a T1w MPRAGE sequence, and completed the full NIHTB-CB. Hippocampal volume was quantified with Freesurfer v7.3.2 and corrected for intracranial volume. Multivariate regressions compared the contributions of age, sex, and unilateral hippocampal volume to neurocognitive outcome by domain; age was examined linearly as well as quadratic and cubic effects given that the developmental course of these areas is likely to be non-linear. Since age and sex were included as predictors, unadjusted standard scores for NIHTB-CB subtests were chosen as dependent variables. Picture Vocabulary (left R^2=.38; right R^2=.39) and Flanker (left R^2=.21; right R^2=.21) scores were significantly associated with greater bilateral hippocampal volume (*ps*<.04), and List Sorting with left hippocampal volume (p=.026, R^2=.15) but not right.

In each model, hippocampal volume and one or more markers of age were significant predictors of neurocognitive outcome, but sex was not. Hippocampal volume did not significantly predict Dimensional Change Card Sorting, Pattern Comparison, Picture Sequence Memory, and Oral Reading scores (*ps*>.05). Scores on all tests, except List Sorting, increased by age across subjects (*ps*<.001). These results expand past adult findings to youth, showing similar relationships between hippocampal volume and neurocognitive tests. Inhibitory control, attention, working memory, and receptive vocabulary appear to be more closely related to hippocampal volume than other subtests. Next steps in this line of research include replicating our findings in clinical samples with known neurocognitive morbidities to determine the degree to which specific neurocognitive deficits, as reflected in NIHTB-CB performance, may reflect the maturation of the hippocampus.

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Poster

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Topic: I.04. Executive Functions

Support: NIH NIMH Grant R01MH131637
FIU UGS Presidential Fellowship

Title: Effects of Age and Social Observation on Theta Synchrony and Its Role in Post-Error Behavior Across Adolescence

Authors: *F. ZAKIROV[1,2], K. HOSSEINI[1,2], A. GARCÍA MORAZZANI[1,2], L. LAPLACE[1,2], J. W. PETTIT[1,2], G. A. BUZZELL[1,2];
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Abstract: Error monitoring allows for detecting mistakes and adapting behavior. Error monitoring is associated with increased theta (4-7 Hz) EEG activity recorded at midfrontal electrode sites located over the medial frontal cortex. Increases in theta synchrony after errors between midfrontal and lateral electrode sites, located over lateral prefrontal, motor, and sensory/parietal brain regions, are associated with post-error behavioral adaptations. However, there is a lack of research into whether such error-related theta inter-regional synchrony dynamics exhibit age-related changes across adolescence and whether such changes differ as a function of social observation. Moreover, there are discrepancies across studies in terms of how error-related theta synchrony between different electrode sites relates to specific forms of post-error adjustments. In this study, we used behavioral and EEG data from 262 adolescents aged 10-14 years who performed a flanker task twice: alone and while observed by a peer. Regardless of social observation, we found age-related increases in error-related midfrontal-frontolateral (p =

.001) and midfrontal-midlateral theta synchrony (p = .001). Additionally, we found that error-related theta synchrony between midfrontal and posterolateral regions increased only in the alone condition (p = .018). Leveraging the shrinking spotlight drift diffusion model (SSP-DDM), we identified a positive association between error-related midfrontal-posterolateral theta synchrony and post-error attentional control (p = .007) but found no effects of social observation. These results are the first to demonstrate that error-related theta synchrony increases from early to mid-adolescence. Additionally, this work specifically links error-related midfrontal-posterolateral theta synchrony to post-error attentional control using computational modeling.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.09/KK57

Topic: I.04. Executive Functions

Support: NIH R21 NS137987

Title: Measuring changes to cortical excitation and inhibition in humans via the TMS-evoked potential

Authors: *K. HUYNH[1], K. HWANG[1], A. D. BOES[2,3,4], C. KELLER[6], J. R. WESSEL[1,3,5]; [1]Psychological and Brain Sci., [2]Pediatrics, [3]Neurol., [4]Psychiatry, [5]Biomed. Engin., Univ. of Iowa, Iowa City, IA; [6]Psychiatry and Behavioral Sci., Stanford Univ., Saratoga, CA

Abstract: Human neuroscience critically depends on non-invasive neural measurements. However, existing methods (fMRI, M/EEG) cannot distinguish whether signal changes result from neural excitation or inhibition (i.e., increased/decreased neuronal firing). For example, invasive recordings from frontal eye field (FEF) neurons show increased firing during memory-guided saccades and decreased firing during proactive anti-saccade inhibition. In fMRI, both processes yield BOLD increases in FEF. Here, we test whether TMS-evoked potentials (TEPs) - EEG features elicited by single-pulse TMS - accurately reflect directional firing changes in the underlying area. Subjects perform memory-guided saccades and proactive anti-saccade inhibition to induce FEF excitation and inhibition, respectively. Individualized FEF hotspots will be identified via BOLD-fMRI. Task-related, fMRI-guided TMS-EEG will then be used to measure TEPs over FEF. We hypothesize that TEPs will increase during memory-guided saccades and decrease during proactive anti-saccade inhibition. This would establish TEPs as the first non-invasive method that distinguishes excitatory from inhibitory neural changes in humans.

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Poster

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Topic: I.04. Executive Functions

Support: NIH Grant R01 DA057312-04

Title: Inhibition-dependent activation within basal ganglia circuitry during stop signal task in adolescents with anxiety symptoms

Authors: *G. E. KIRKPATRICK[1], J. R. COHEN[2], D. H. FISHBEIN[3], A. BELGER[4]; [1]Psychiatry, Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; [2]Dept. of Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]FPG Child Develop. Inst., Penn State Univ., Chapel Hill, NC; [4]Univ. of North Carolina, Chapel Hill, NC

Abstract: Diverging developmental trajectories of inhibitory control during adolescence are hypothesized to impact vulnerability to psychiatric disorders such as substance use and anxiety. The diverse array of anxiety-related symptoms can result in diverging inhibition phenotypes and altered neural underpinnings. In people with obsessive compulsive disorder and high anxiety, inhibitory control is associated with disruption to the basal ganglia. Alterations across nodes from the three cortico-basal-ganglia pathways (direct, indirect, and hyper-direct) have been implicated in diverse inhibition phenotypes. Yet, it is unknown how these pathways function in an adolescent population with anxiety. Here, we aim to replicate neural signatures associated with stop signal task (SST) found in Isherwood et al., 2025 and examine how activated regions associated with the basal ganglia pathways during SST are differentially correlated with self-reported anxiety symptoms in early adolescence. 71 adolescents (12-14) with varying levels of anxiety completed the SST during 3T fMRI scanning. Beta values were extracted from ROIs related to the indirect pathway (caudate, putamen, thalamus, red nucleus, substantia nigra, subthalamic nucleus, and the globus pallidus internal and external) and the hyper-direct pathway (subthalamic nucleus, globus pallidus internal, substantia nigra, and thalamus). Mean stop signal reaction time (SSRT) was used as a measure of inhibition and the anxiety subscale from the ALEXSA was used as the anxiety variable. Results replicated Isherwood et al, with conditions related to failed inhibitory control activating nodes in the indirect pathway, while conditions related to successful inhibition activated the inferior frontal gyrus, thalamus, and ventral tegmental area, implying that the indirect pathway may be involved in failed inhibitory control in adolescents. Anxiety correlated positively with longer SSRT (*r=0.304; p=0.009*) implying that anxiety was related to greater inhibition. Regarding the neural activation, anxiety correlated positively with nodes in the indirect pathway for conditions associated with failed (*r=0.573; p=0.013*) and successful inhibition (*r=0.525; p=0.038*) indicating that anxiety might be linked to activity in the indirect pathway during both failed and successful inhibition. Future directions include assessing the relationship between anxiety symptoms and basal ganglia pathway activation as well as functional connectivity between the nodes.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

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Program #/Poster #: PSTR331.11/KK59

Topic: I.04. Executive Functions

Support: NSF 2342319

Title: Probing the temporal dynamics of the neural representations underlying cognitive control during conflict resolution

Authors: *J. SELLERS, J. A. BRISSENDEN, H. ZHANG, J. JONIDES, T. G. LEE;
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Abstract: Cognitive control refers to the collection of processes that allow us to engage in goal-directed behavior when habits come into conflict with our goals. Classic tasks used to study the conflict resolution process put task-irrelevant information into conflict with task-relevant information. For example, in the arrow Simon task, participants are instructed to respond to the direction of an arrow. The location of this arrow can be incongruent or congruent to its direction, allowing researchers to test for differences in behavior and neural activity when conflict is present or not. A large body of work has identified the neural correlates of the conflict resolution process, and neurocomputational models of cognitive control have ascribed distinct functional roles to brain regions within frontal and parietal cortices. However, virtually all this research has relied on tasks that use free response times (RTs) as the primary dependent variable, which are known to introduce a time-on-task confound for functional magnetic resonance imaging (fMRI) studies. Incongruent trials typically have longer RTs than congruent trials, so it is unclear if univariate fMRI contrasts of incongruent and congruent trials truly reflect a differential engagement of neural processes or the same engagement but for longer periods of time. To explicitly address the time-on-task confound and to more directly probe the time course of conflict resolution processes, we applied the forced-response method to an arrow Simon task while participants underwent an fMRI scan. The forced-response method involves fixing RT and varying stimulus onset, allowing us to control processing time (PT). Participants performed congruent and incongruent trials with three stimulus onset times. These stimulus onset times reflect a time when habitual processing is complete but goal-directed processing is not (short PT), an intermediate time when goal-directed processing is beginning to override habitual output (medium PT), and a time when goal-directed processing has overridden habitual processing (long PT). Univariate contrasts of incongruent and congruent trials at the same PT reveal that differences in activity in frontoparietal regions are largely present at short PTs and disappear at long PTs. Using representational similarity analysis (RSA), we characterize the representations underlying the conflict resolution process in these regions and examine how adjustments in

control affect these representations. These results demonstrate that the forced-response method can be used to directly control for time-on-task confounds and highlight the time dependent nature of conflict resolution processes.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.12/KK60

Topic: I.04. Executive Functions

Title: Neural Mechanisms of Proactive and Reactive Control in AX-CPT

Authors: *O. R. MILNE[1], L. LIUZZI[1], D. S. PINE[1], P. KHOSRAVI[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]The Catholic Univ. of America, Falls Church, VA.

Abstract: Introduction
Inhibitory control (IC) is a core executive function that facilitates goal-directed behavior by suppressing responses to irrelevant stimuli. It comprises two distinct processes: proactive control, involving the selection and maintenance of goal-relevant information, and reactive control, involving the retrieval of necessary contextual information. Both can be measured by the AX Continuous Performance Task (AX-CPT). Because IC is often impaired in individuals with anxiety disorders, understanding its processes is vital in conceptualizing anxiety's proactive (preparation for potential threats) and reactive (response to immediate threats) components. The present study aimed to examine the convergence and distinction between proactive and reactive control in neural function.
Methods
Thirty-six adults (M age = 39 +/- 13) completed the AX-CPT task while undergoing fMRI scanning. The task presented cue–probe letter sequences, during which a frequent target condition (AX) and less frequent non-target conditions (AY, BX, BY) appeared at random, probing proactive and reactive cognitive control dissociably. The task had 4 runs, each lasting 20 minutes. Imaging data was preprocessed using Analysis of Functional NeuroImages (AFNI), and group-level analyses were conducted using 3dttest++, comparing A-cue vs B-cue trials (proactive vs reactive cue processing) and AX vs BX probe trials (proactive control demands). Statistical maps were thresholded at $p < .005$ and cluster-corrected ($k = 55$) to control for multiple comparisons.
Results
The AX vs BX probe contrast revealed 23 significant clusters, including activation in the bilaterial postcentral gyrus, bilateral middle frontal gyrus, bilateral middle cingulate cortex, and left anterior cingulate cortex. The A vs B cue contrast revealed 7 significant clusters, including activation in the right angular gyrus, right middle frontal gyrus, left postcentral gyrus, left middle

frontal gyrus, and left precentral gyrus.

Discussion

Findings indicate that proactive and reactive control involve overlapping regions of fronto-cingulate networks, including the middle frontal gyrus and cingulate cortex, suggesting an overlapping executive control process. However, proactive control showed greater associations with widespread frontal and cingulate network activity, while reactive control demonstrated more parietal involvement, reflecting functional separation between the two processes. These results enhance our understanding of inhibitory control mechanisms, and will continue to inform an ongoing investigation involving the relation between anxiety and IC in pediatric samples.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

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Program #/Poster #: PSTR331.13/KK61

Topic: I.04. Executive Functions

Title: Degradation of attentional inhibition function following high cognitive load: An MMN study

Authors: *T. KAMBARA[1], S. ATARASHI[1], C. XU[1], T. TERUNUMA[1], T. URAKAWA[2], O. ARAKI[1];
[1]Tokyo Univ. of Sci., Katsushika-ku, Tokyo, Japan; [2]Mazda Motor Corp., Hiroshima, Japan

Abstract: From Attentional Control Theory, individuals with high trait anxiety are susceptible to task-irrelevant sensory changes due to degradation of inhibitory function when they performed a behavioral task (Eysenck et al., 2007). This degradation is reported to be captured by enlargement of mismatch negativity (MMN) (Urakawa et al., 2026) which is a pre-attentive brain response to task-irrelevant auditory sensory changes. On the other hand, cognitive fatigue generally decreases brain activity related to attention as fMRI studies reported (Lim et al., 2010). Taking this perspective, the present study tested a hypothesis that fatigue-like degradation of inhibition function immediately following a high cognitive load would appear; specifically, we attempted to determine whether such degradation would be measured by persistent MMN's enlargements following the high cognitive load especially for anxiety-prone individuals. Sixteen participants (mean age = 22.0 years, SD = 1.7) performed N-back tasks (N = 1, 3) with task-irrelevant auditory oddball stimuli (1300/1000 Hz). The order of the tasks was as follows: 1-back (1b-ref), 3-back (3b) 5 minutes after 1b-ref, 1-back task (1b-1) immediately after 3b offset, 1-back (1b-2) 15 minutes after 3b offset, and 1-back (1b-3) 30 minutes after 3b offset. A two-way repeated measures ANOVA on the behavioral data revealed a significant main effect of task condition on both accuracy ($F(4, 52) = 18.115$, $p < .001$) and reaction times ($F(4, 52) = 49.230$, $p < .001$). Post-hoc tests with the Bonferroni correction indicated that the 3-back condition showed decreased accuracy and prolonged reaction times compared with the 1-back conditions, whereas

no significant differences were found among the 1-back conditions. EEG analysis revealed that the difference in MMN amplitude (latency: 50-200 ms) between 1b-1 and 1b-ref significantly correlated with STAI-T scores (r = -0.65, p < 0.05), whereas the MMN amplitude differences between the target task (3b, 1b-2, or 1b-3) and 1b-ref did not significantly correlate with STAI-T scores. These findings indicate that trait-anxiety-dependent attenuation of inhibitory function occurs immediately after, rather than during, the high cognitive load task, and it persists for approximately 10 minutes. These findings suggest an evaluation method of attentional inhibition function that is expected to be reflected in the difference of MMN amplitudes during a low-cognitive-load task within 10 minutes after a high-cognitive-load task.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.14/Web Only

Topic: I.04. Executive Functions

Title: Acute Effects of Breathing Combined with Oculomotor Priming on Executive Conflict Processing

Authors: *S. A. MANEY[1], V. R. SHANKAR[2,1], J. PUNETHA[1];
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Abstract: Executive control enables suppression of task-irrelevant information during goal-directed behaviour. Although breathing regulation and oculomotor activity have individually been linked to attentional processes, little is known about their combined acute effects on conflict processing. This study examined the effects of breathing combined with oculomotor priming on Flanker-task performance. Trained young adult athletes with no known cognitive or musculoskeletal conditions (N = 27, 6 F; aged 21.3 ± 1.8 years) completed randomised, counterbalanced crossover conditions consisting of control (CON), breathing regulation (BR), and breathing regulation plus oculomotor priming (BROC). All conditions included the control warm-up (2-min jog, 10 squats, and 10 walking lunges). BR added 2 min of guided 4:6 breathing, and BROC added 2 min of guided 4:6 breathing plus five oculomotor exercises lasting approximately 2.5 min. Executive conflict processing was assessed using a computerized Eriksen Flanker task. Interference cost (IC) was calculated as the difference between incongruent and congruent median reaction times derived from correct trials only. Non-parametric analyses were performed because several IC variables violated assumptions of normality. A significant condition effect was observed for IC ($\chi^2(2)=13.56$, P<0.001, Kendall's W=0.25). Post hoc Wilcoxon analyses demonstrated lower IC during BROC compared with CON (P<0.001, r=0.71)

and BR ($P<0.05$, $r=0.46$), whereas no difference was observed between CON and BR (P=n.s., $r=0.33$). Median IC was 78.00 ms (95% bootstrap CI: 53.00-96.00) during CON, 58.80 ms (95% bootstrap CI: 55.00-82.00) during BR, and 51.50 ms (95% bootstrap CI: 43.00-64.00) during BROC. Accuracy exceeded 95% across all testing sessions and did not differ between conditions ($\chi^2(2) =0.39$, P=n.s.). Breathing combined with oculomotor priming was associated with reduced Flanker interference cost compared with control and breathing regulation alone, without compromising response accuracy.

Disclosures: S.A. Maney: None. **V.R. Shankar:** None. **J. Punetha:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.15/KK62

Topic: I.04. Executive Functions

Support: NIH Grant 5R21HD110656

Title: The acute effects of high-intensity interval training with versus without mindfulness during recovery intervals on children's executive function and underlying neuroelectric physiology

Authors: *S.-C. KAO[1], M. CORTES OSPINA[2], K. NOH[2];
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Abstract: High-intensity interval training (HIIT) has acute beneficial effects on children's inhibitory control (IC) and underlying attention allocation process manifested by the P3 component of event-related brain potentials (ERPs). However, most studies did not consider the potential use of recovery intervals during HIIT for further IC enhancement. Because mindfulness (MF) also has acute benefits to IC and associated conflict monitoring processes evidenced by the N2-ERP component, this study examined whether incorporating MF into recovery intervals of HIIT can synergistically maximize the IC-enhancing effect in children. Using a within-subject crossover design, 52 children (28 girls, 11.3 ± 0.9 years) completed a flanker task with concurrent electroencephalogram (EEG) to measure accuracy, response time (RT), and N2/P3 ERP outcomes of IC before and after a 20-min session of MF-HIIT, HIIT-only, MF-only, and rest control conditions on separate days in counterbalanced order. The treadmill-based MF-HIIT condition included a 1.5-min warm-up, six 1.5-min running exercise intervals over 76% of maximum heart rate separated by five 1.5-min walking recovery intervals, and a 2-min cool-down. Participants were provided with MF cues during the warm-up, recovery intervals, and cool-down to induce state-related MF. Participants received a similar amount of MF cues while sitting during the entire MF-only condition. During the HIIT-only condition, participants completed the same warm-up, exercise/recovery, and cool-down activities but did not receive MF cues. During the control condition, participants remained seated while watching a health-

related educational video without engaging in HIIT or MF cues. The analysis showed that the MF-only condition resulted in increased RT from pretest to posttest and longer RT than the other conditions at posttest, while P3 amplitude decreased from pretest to posttest following interventions involving MF, including MF-HIIT and MF-only conditions. Although the MF cues employed in this study alone led to an ineffective pattern of neuroelectric activity and IC performance (e.g., reduced availability of attention resources and slower responses), integrating these brief MF cues into HIIT recovery resulted in superior neural efficiency. That is, less allocation of attention to stimulus evaluation in facilitating IC performance outcomes that were comparable with traditional HIIT and control. These findings suggest that MF-HIIT is a feasible strategy to alter neuroelectric brain function in support of IC performance while promoting health behaviors such as MF and physical activity.

Disclosures: S. Kao: None. **M. Cortes Ospina:** None. **K. Noh:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.16/KK63

Topic: I.04. Executive Functions

Support: Wild Blueberry Association of North America
The Peanut Institute
Georgia State University

Title: Association between estimated Visceral Adipose Tissue and Executive Function in Female Adults with Pre-diabetes

Authors: *S. K. FERNANDES[1], C. M. MCCARTHY[2], J. P. DANH[2], M. KHEIM[5], J. PINCUS[3], A. SRSICH[3], T. Z. KING[6,3], R. G. FERESIN[4];
[1]Biology/Nutrition, [2]Chemistry/Nutrition, [3]Psychology, [4]Nutr., Georgia State Univ., Atlanta, GA; [5]Biol., Georgia State Univerisity, Atlanta, GA; [6]Nell Hodgson Sch. of Nursing, Emory Univ., Atlanta, GA

Abstract: Introduction
Pre-diabetes, characterized by insulin resistance, is associated with increased risk of cognitive impairment. Visceral adipose tissue is metabolically active and contributes to systemic inflammation, oxidative stress and insulin resistance, all of which have been implicated in cognitive decline. Executive function appears vulnerable to metabolic dysfunction; however, the relationship between visceral adiposity and executive function in women with pre-diabetes remains poorly understood. This pilot study investigated associations between estimated visceral adipose tissue (eVAT) and executive function in adult women with pre-diabetes.
Methods
A cross-sectional pilot study was conducted in 13 adult women with pre-diabetes (FBG 100-125

mg/dL and/or HbA1c 5.7-6.4%). Participants had a median age of 55 years (IQR: 46-64), mean BMI of 29.25 ± 1.14 kg/m² and mean FBG of 104.92 ± 8.04 mg/dL. eVAT mass (mean = 1.06 ± 0.68 kg) was estimated by dual-energy X-ray absorptiometry . Executive function was assessed using the D-KEFS Verbal Fluency (VF), Color-Word Interference (CWI), and NIH Toolbox Dimensional Change Card Sort (DCCS). Pearson's or Spearman's correlations were used as appropriate. Statistical significance was set at $p < 0.05$ uncorrected for multiple comparisons due to the exploratory nature of this pilot study

Results

Higher eVAT was inversely associated with measures of executive function, including cognitive flexibility assessed by D-KEFS CWI Inhibition/Switching ($r = -0.620$, $p = 0.024$), VF Switching Accuracy ($r = -0.574$, $p = 0.040$) and NIH Toolbox DCCS ($r = -0.596$, $p = 0.04$), as well as inhibitory control assessed by D-KEFS CWI Inhibition ($r = -0.656$, $p = 0.015$). No significant associations were observed with other cognitive measures.

Conclusion

Higher eVAT was consistently associated with poorer performance across measures of executive function, particularly cognitive flexibility and inhibitory control in adult women with pre-diabetes. Consistent results across three independent cognitive assessments strengthen this finding despite the small sample size. These findings are consistent with proposed mechanisms linking visceral adiposity and insulin resistance to executive function. Although causal inference cannot be made due to the cross-sectional design and limited sample size, observed effect sizes suggest that visceral adiposity may be an important contributor to early cognitive vulnerability in women with pre-diabetes. Larger longitudinal and intervention studies are needed to determine if reducing visceral adiposity can preserve executive function and mitigate cognitive decline in women with pre-diabetes.

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.17/Web Only

Topic: I.04. Executive Functions

Support: Simons Foundation ARI #220843

Title: Neurophysiological changes in cognitive control in healthy aging and Alzheimer's disease

Authors: *J. D. SENTA[1], C. L. DALE[4], F. SYED[2], T. L. LUKS[3], J. KRAMER[2], E. H. SHERR[2], K. RANKIN[2], S. NAGARAJAN[5], K. RANASINGHE[6];
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Imaging, San Francisco, CA; [5]Radiology and Biomed. Imaging, Univ. of California, San Fransisco, San Francisco, CA; [6]Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract: Cognitive control shows a complex pattern of change in normal aging and is among the earliest functions disrupted in Alzheimer's disease (AD), yet its neurophysiological basis across the aging and disease continuum remains poorly characterized. We used magnetoencephalography (MEG) neuroimaging during a cognitive Stroop color-naming task to test the neurophysiological response to conflict control in 54 healthy controls aged 18-59 (HC), 19 healthy older adults aged ≥60 (HO), and 15 patients with AD. Source-localized incongruent-vs-congruent contrasts were computed over the ~600ms encoding interval for theta (3-7 Hz), alpha (8-12 Hz), beta (12-30 Hz), and high-gamma (63-117 Hz) frequency bands. Temporally persistent clusters (≥100 ms, ≥20 voxels) identified in HC were used to extract individual mean and peak activations in all groups, which were correlated with accuracy, response time (RT), and inverse efficiency (IES); group differences were tested with Fisher z.
In HC, conflict-related activation (incongruent vs. congruent) tracked performance with regional and spectral specificity. Higher theta in left inferior parietal and lateroventral cortex, higher alpha in left superior temporal gyrus, and reduced beta suppression in right inferior frontal gyrus each predicted faster RT and better IES; reduced high-gamma suppression in right midfrontal gyrus and reduced beta suppression in right superior frontal gyrus predicted higher accuracy. In healthy aging, theta-behavior correlations reversed: higher theta predicted slower RT and worse efficiency in HO versus HC (Fisher $z=-3.6$, $p<.001$). AD instead diverged from both younger and older controls at a distinct locus, right midfrontal gyrus, where stronger alpha and high-gamma responses tracked worse performance (slower RT, lower accuracy), unlike the near-zero coupling in either healthy group (Fisher z up to 3.3). This frontal divergence was anatomically consistent across both comparisons and bands (8 of 9 divergent correlations), distinguishing AD from both younger and older HC and dissociating the disease signature from healthy aging. These findings suggest cognitive control depends on parietal and temporal oscillatory coupling that is retuned in healthy aging and disrupted by a distinct right-frontal signature in AD.

Disclosures: J.D. Senta: None. **C.L. Dale:** None. **F. Syed:** None. **T.L. Luks:** None. **J. Kramer:** None. **E.H. Sherr:** None. **K. Rankin:** None. **S. Nagarajan:** None. **K. Ranasinghe:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.18/KK64

Topic: I.04. Executive Functions

Title: Relationship between Trait Anxiety and Theta-Band ITPC of the Mismatch Oscillatory Response under Cognitive Load

Authors: *S. ATARASHI[1], T. KAMBARA[1], C. XU[1], T. URAKAWA[2], T. TERUNUMA[1], O. ARAKI[1];
[1]Dept. of Applied Physics, Tokyo Univ. of Sci., Katsusika-ku, Tokyo, Japan; [2]Mazda Motor Corp., Hiroshima, Japan

Abstract: Attentional Control Theory suggests that individuals with higher trait anxiety have difficulty suppressing task-irrelevant stimuli, resulting in the dominance of stimulus-driven processing during attentionally demanding tasks (Eysenck et al., 2007). Previous studies have suggested that stimulus-driven neural processing underlying orienting responses to auditory changes is reflected in theta-band inter-trial phase coherence (ITPC) of the mismatch oscillatory response (MOR) (Fuentemilla et al., 2007; Urakawa et al., 2026). Based on these findings, we hypothesized that individuals with higher trait anxiety would show increased MOR ITPC-θ during attentionally demanding tasks that reflects enhanced stimulus-driven neural processing underlying orienting responses to task-irrelevant auditory changes. To test this hypothesis, participants (N=20; mean age =22.1 years, SD=1.69) performed a 1-back task followed by a 3-back task while task-irrelevant auditory oddball stimuli were presented (DEV: 1000 Hz or 1300 Hz). MOR ITPC-θ was analyzed in the left and right fronto-central and parietal regions between 100 and 300 ms after the auditory stimulus onset. The results showed that, in the 1300 Hz condition, MOR ITPC- θ was significantly positively correlated with STAI-T scores in the parietal regions during the 1-back task (left parietal: $r = 0.70$, $p < 0.005$; right parietal: $r = 0.62$, $p < 0.005$) . This suggests that individuals with higher trait anxiety may show enhanced stimulus-driven neural processing underlying orienting responses to task-irrelevant auditory changes under low cognitive load. In contrast, no significant correlation between MOR ITPC-θ and STAI-T scores was observed during the 3-back task. Furthermore, a linear regression model including the interaction between STAI-T score and task difficulty revealed a significant interaction in the left parietal region ($\beta = -0.0032$, $p < 0.05$) and an interaction tendency in the right parietal region ($\beta = -0.0027$, $p = 0.06$). Simple-slope analyses showed that individuals with lower trait anxiety tended to show increased MOR ITPC-θ from the 1-back to the 3-back task (left parietal: $\beta = 0.034$, $p = 0.13$; right parietal: $\beta = 0.039$, $p = 0.08$), whereas individuals with higher trait anxiety tended to show decreased MOR ITPC-θ (left parietal: $\beta = -0.037$, $p = 0.09$; right parietal: $\beta = -0.021$, $p = 0.33$). These findings suggest that, as cognitive load increases, individuals with lower trait anxiety may show increased stimulus-driven neural processing underlying orienting responses to task-irrelevant auditory changes, whereas individuals with higher trait anxiety may have difficulty maintaining such processing.

Disclosures: S. Atarashi: None. **T. kambara:** None. **C. Xu:** None. **T. Urakawa:** A. Employment/Salary (full or part-time):; Mazda Motor Corporation. **T. terunuma:** None. **O. Araki:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.19/KK65

Topic: I.04. Executive Functions

Support: NIH Grant AI153130
NICHD Grant P50HD105353

Title: Early regional brain volume differences predict long-term differences in inhibitory behaviors in rhesus macaques prenatally exposed to Zika virus

Authors: *J. GUTKES[1], N. PATEL[1], E. RAZO[1], V. PRABHAKARAN[2], R. VLASOVA[3], A. ADLURU[1], N. ADLURU[1], E. MOHR[1], K. AUSDERAU[1];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Dept Neurosci, Univ. of Wisconsin, Madison, WI; [3]Psychiatry, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Prenatal exposure to Zika virus (ZIKV) is a serious health concern due to ZIKV's effect on infant neurodevelopment, potentially affecting language, cognition, and motor development. While severe cases of prenatal ZIKV exposure result in congenital abnormalities that are evident at birth (9%), mild neurodevelopmental deficits (30%) in normocephalic infants are often not identified until later in life. To define cognitive and behavioral deficits after prenatal ZIKV exposure, we used a rhesus macaque model comparing ZIKV-exposed infants to mock-injection controls. Using a spatial planning task, the puzzle feeder, the macaques' cognitive performance and inhibitory behaviors were measured by highest level achieved and number of attempts, respectively at 30 months. We also performed T1 weighted and T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) at 1, 3, and 12 months to assess volumetric differences in the brain after prenatal ZIKV exposure. ZIKV-exposed macaques showed no differences in cognitive performance or inhibitory behaviors on the puzzle feeder at 30 months (ZIKV n=25, control n=10). ZIKV-exposed macaques had inconsistent volumetric differences in MRIs at 1 month (ZIKV n= 12, control n=5) and 3 months (ZIKV n=29, control n=9) but no differences were detected at 12 months (ZIKV n=29, control n=11). At 1 month ZIKV-exposed macaques displayed significantly increased grey matter (GM) in the cingulate (p=.006) and insular cortices (p=.030), decreased GM in the occipital cortex (p=.015), increased white matter (WM) in the cerebellum (p=.045), and decreased cerebrospinal fluid in the lateral ventricles (p=.045). At 3 months ZIKV-exposed macaques had significantly increased WM in the insular cortex (p=.036) and corpus callosum (p=.034) while having reduced WM in the frontal lobe (p=.003). To examine the relationship between early (1 month) volumetric differences and later cognitive outcomes at 30 months, a linear regression was performed, comparing regional volumes to the highest level achieved and total number of attempts on the puzzle feeder. We found a significant relationship between cingulate cortex GM volume at 1 month of life and the total number of attempts made on the puzzle feeder (p=.018) with a weak correlation of r=0.14. We did not identify any other significant relationships between regional brain volumes and cognitive or inhibitory outcomes. Overall this data suggests that early volumetric differences have the potential to identify infants that may be at risk for later in life neurodevelopmental deficits, but volumetric differences may only be present early in life.

Disclosures: J. Gutkes: None. **N. Patel:** None. **E. Razo:** None. **V. Prabhakaran:** None. **R. Vlasova:** None. **A. Adluru:** None. **N. Adluru:** None. **E. Mohr:** None. **K. Ausderau:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.20/Web Only

Topic: I.04. Executive Functions

Support: MH59299

Title: Increased functional heterogeneity of frontal sub-networks during motor control in OCD: Applications of Agglomerative Hierarchical Clustering of fMRI time series

Authors: *I. DAXINI[1], H. SAAD[2], J. HADOUS[3], D. R. ROSENBERG[5], J. A. STANLEY[4], V. A. DIWADKAR[6];
[1]Case Western Reserve Univ., Cleveland, OH; [2]Wayne State Univ., Dearborn Heights, MI; [3]Wayne State Univ., Dearborn, MI; [4]Psych & Behav Neurosci, Wayne State Univ., Detroit, MI; [5]Dept Psychiatry, Wayne State Sch. Med., Detroit, MI; [6]Psychiatry & Behavioral Neurosci., Wayne State Univ. SOM, Detroit, MI

Abstract: Obsessive-compulsive disorder (OCD) is characterized by altered cortico-striatal-thalamo-cortical circuitry that may impact behavioral processes related to motor and cognitive control (Rosenberg & Keshavan, 1998). Frontal brain regions are therefore likely to be heavily implicated during behavioral processes that involve motor excitation and motor inhibition (Paus, 2001). Here to assess differences in the nature of frontal lobe involvement in OCD (relative to healthy controls, HC) we applied agglomerative hierarchical clustering (AHC)(Murtagh & Legendre, 2014) to fMRI time series data collected using an established motor control paradigm (Go/No-Go)(Woodcock et al., 2025). Our goals were to parcellate brain regions into sub-networks, and to compare the assignment of frontal regions to sub-networks in OCD and HC. fMRI data were acquired in 82 participants (OCD=42, HC=40). Time series were extracted from regions defined using a cerebral parcellation scheme (Fan et al., 2016) in each participant and condition (Go and No-Go), were standardized for each region and averaged across participants within each group. Time series from each group and condition were then clustered using AHC. The optimal number of partitions (i.e., sub-networks) were identified using the Kneedle algorithm (Satopa et al., 2011). In HC, for each of the Go and No-Go conditions, the 46 frontal regions in the connectome were assigned equally into two clusters (Go-HC_{C1}, Go-HC_{C2} and NoGo-HC_{C1}, NoGo-HC_{C2}), where membership in the larger cluster (C1) was shared with regions from across the cerebral space (temporal, parietal, insular, limbic, occipital, sub-cortical). In OCD by comparison, we observed highly fractionated assignment of the 46 frontal regions: while in each condition a high percentage of frontal regions (Go-OCD_{C1}=47% and NoGo-OCD_{C1}=67% respectively) were assigned to clusters with very high structural resemblance to HC_{C1}, the remainder were assigned across the partitioned sub-networks. The entropy of the mean time series in each sub-network was taken to represent the stability of the sub-network's functional role (low entropy = functionally stable sub-networks)(Bhatt et al., 2025). In each of the HC and OCD groups, the frontal heavy sub-networks evinced low entropy relative to their counterparts, underlining the importance of the frontal cortex and its connectivity patterns to ongoing functional operations related to executive function, monitoring and attention (Catani,

2019). While a modicum of this is preserved in OCD, it appears that frontal regions evince greater functional heterogeneity in this disorder.

Disclosures: I. Daxini: None. **H. Saad:** None. **J. Hadous:** None. **D.R. Rosenberg:** None. **J.A. Stanley:** None. **V.A. Diwadkar:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.21/LL1

Topic: I.04. Executive Functions

Title: Caffeine produces unique side effects in those with attention-deficit/hyperactivity disorder

Authors: M. GONZALEZ HERNANDEZ, ***J. A. BOYETTE-DAVIS**;
St. Edward's Univ., Austin, TX

Abstract: Caffeine is widely reported to produce paradoxical sedative effects in individuals with Attention-Deficit/Hyperactivity Disorder (ADHD), yet this claim has not been empirically tested in published research. The present study used a cross-sectional online survey to examine whether self-reported ADHD symptoms and ADHD status were associated with greater caffeine-induced sleepiness and distinct caffeine use patterns in adults, with general daytime sleepiness on the Epworth Sleepiness Scale included as a secondary measure. Participants (N = 79; Medium age = 32.97, SD = 17.26) completed validated measures including the Adult ADHD Self-Report Scale (ASRS v1.1), the Epworth Sleepiness Scale (ESS), the Patient Health Questionnaire-2 (PHQ-2), and the Generalized Anxiety Disorder-2 (GAD-2), alongside custom items assessing caffeine use and perceived caffeine-induced side effects. Participants with ADHD (diagnosed or self-suspected; n = 33) reported significantly greater levels of sleepiness after caffeine consumption compared to those without ADHD. ASRS total scores correlated positively with caffeine-induced sleepiness, and with ESS total scores. Daily caffeine intake differed significantly between groups, specifically those with ADHD consumed less caffeine than those without this diagnosis. These findings offer the first empirical support for the widely reported but previously untested phenomenon of caffeine-induced sedation in individuals with ADHD symptoms and lay the groundwork for future mechanistic investigations.

Disclosures: M. Gonzalez Hernandez: None. **J.A. Boyette-Davis:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.22/LL2

Topic: I.04. Executive Functions

Title: Executive function and treatment adherence in adults with type 2 diabetes mellitus

Authors: *Y. G. VILLALPANDO CHAGOLLA[1], N. Y. CORTÉS[2], L. LUNA-VILLEGAS[3]; [1]Dept. de Enfermería y Obtetricia, Univ. de Guanajuato, División de Ciencias Naturales y Exactas, Guanajuato, Mexico; [2]Nursing and Midwifery, [3]Univ. de Guanajuato, Guanajuato, Mexico

Abstract: Introduction: Type 2 diabetes mellitus (T2DM) is a global public health problem whose high prevalence and associated complications significantly impact patients' quality of life. Chronic hyperglycemia, insulin resistance, and related vascular changes may lead to alterations in higher cognitive functions, particularly executive function, potentially compromising the patient's ability to follow therapeutic instructions, remember medications, and sustain self-care behaviors. **Objective:** To analyze the relationship between executive functions and treatment adherence in adults with T2DM, considering components of therapeutic self-management and glycemic control through glycated hemoglobin (HbA1c). **Methods:** A quantitative, observational, analytical, and cross-sectional study was conducted. A sample of 20 adults diagnosed with T2DM was evaluated. Executive function was assessed using the Neuropsychological Battery of Executive Functions and Frontal Lobes (BANFE-3) and the Frontal Assessment Battery (FAB). Treatment adherence and self-care behaviors were measured using the Summary of Diabetes Self-Care Activities (SDSCA). Glycemic control was determined through HbA1c levels as an indicator of average blood glucose over the preceding two to three months. **Results:** Of the 20 participants (mean age: 54.3 ± 9.1 years; 60% women), 45% showed scores in the mild-to-moderate impairment range in at least one BANFE-3 domain, with the greatest involvement in planning (40%) and inhibitory control (35%). Mean FAB score was 13.2 ± 2.4 (cutoff ≥12). On the SDSCA, the dimensions with the lowest adherence were physical exercise (mean: 2.1 days/week) and blood glucose monitoring (mean: 2.8 days/week), while medication adherence was the highest (mean: 5.6 days/week). Mean HbA1c was 8.4 ± 1.3%, indicating poor glycemic control in 70% of participants. A statistically significant negative correlation was found between BANFE-3 scores and overall SDSCA adherence ($r = -0.62$, $p < 0.01$), as well as between HbA1c and total FAB score ($r = -0.48$, $p < 0.05$). **Conclusions:** The findings suggest that lower executive function performance is associated with poorer treatment adherence in adults with T2DM. Impairments in planning and inhibitory control may represent a cognitive barrier to effective disease self-management.

Disclosures: Y.G. Villalpando Chagolla: None. **N.Y. Cortés:** None. **L. Luna-Villegas:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.23/LL3

Topic: I.04. Executive Functions

Title: Cognitive-Social Intervention Improves Executive Function and Psychosocial Well-Being in Breast Cancer Survivors: A Community-Based Pre-Post Study

Authors: *N. Y. CORTÉS[1], C. R. VUELVAS-OLMOS[2], L. LUNA-VILLEGAS[1];
[1]Univ. de Guanajuato, Guanajuato, Mexico; [2]Neurosci., Univ. of Guanajuato, Romita, Mexico

Abstract: Introduction: Cancer-related cognitive impairment (CRCI), emotional distress, and reduced social support are common among breast cancer survivors and may persist long after treatment completion. Non-pharmacological interventions targeting cognitive and psychosocial functioning have emerged as promising strategies to address these challenges. This study evaluated the effects of a community-based cognitive-social intervention on executive function, emotional well-being, and perceived social support in breast cancer survivors. **Methods:** A pre-post intervention study was conducted in 150 breast cancer survivors participating in a community support program. Participants completed a 10-session cognitive-social intervention integrating cognitive stimulation, autobiographical memory exercises, problem-solving activities, mindfulness practices, artistic expression, and structured social interaction. Executive function was assessed using the Neuropsychological Battery of Executive Functions and Frontal Lobes (BANFE). Emotional well-being was evaluated through measures of depression (PHQ-9), anxiety (GAD-7), and perceived stress (PSS-10). Perceived social support was assessed using the MOS Social Support Survey. **Results:** Following the intervention, participants demonstrated improvements in executive function (BANFE: 84.6 to 91.2; $\Delta = +6.6$) and perceived social support (MOS: 66.7 to 74.7; $\Delta = +8.0$). Reductions were observed in depressive symptoms (PHQ-9: 8.1 to 6.4; $\Delta = -1.7$), anxiety symptoms (GAD-7: 7.6 to 5.5; $\Delta = -2.1$), and perceived stress (PSS-10: 20.3 to 17.0; $\Delta = -3.3$). Improvements were observed across cognitive, emotional, and social domains following participation in the intervention. **Conclusions:** A community-based cognitive-social intervention was associated with improvements in executive functioning, emotional well-being, and perceived social support among breast cancer survivors. These findings support the potential value of multidimensional interventions for addressing CRCI and psychosocial challenges during survivorship and highlight the relevance of community-based approaches for promoting cognitive and emotional recovery after cancer treatment.

Disclosures: N.Y. Cortés: None. **C.R. Vuelvas-Olmos:** None. **L. Luna-Villegas:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.24/Web Only

Topic: I.04. Executive Functions

Title: Correlation between impulsiveness scores and theta/beta ratio in individuals with ADHD symptoms differs between subjects with and without hazardous alcohol consumption

Authors: W. HERRERA-MORALES[1], J. V. REYES -LOPEZ[3], *L. NUÑEZ-JARAMILLO[2]; [1]Dept. de Ciencias Médicas, División de Ciencias de la Salud. Univ. Autónoma del Estado de Quintana Roo, Chetumal, Mexico; [2]División de Ciencias de la Salud. Univ. Autónoma del Estado de Quintana Roo, Chetumal, Quintana Roo, Mexico; [3]Univ. Autónoma de Querétaro / Psiquiatría Integral Juriquilla, Querétaro, Mexico

Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder commonly diagnosed during childhood; however, more than 60% of children with ADHD continue to exhibit symptoms into adulthood. ADHD is frequently accompanied by psychiatric comorbidities, which may influence its clinical and neurophysiological manifestations. In the present study, we assessed impulsivity and the theta/beta ratio in individuals with ADHD symptoms, individuals with ADHD symptoms and hazardous alcohol consumption, and healthy controls. We observed a significant positive correlation between motor impulsivity scores and the theta/beta ratio in the frontal region among participants with ADHD symptoms alone, whereas this association was not observed in individuals with both ADHD symptoms and hazardous alcohol consumption or in controls. Additionally, non-significant trends toward correlations between cognitive and non-planning impulsivity scores and the theta/beta ratio were observed in the centroparietal and temporo-occipital regions, exclusively among participants presenting ADHD symptoms without hazardous alcohol consumption. These findings suggest that the relationship between impulsivity-related cognitive processes and brain electrical activity in individuals with ADHD is altered by the presence of hazardous alcohol consumption. Our results underscore the importance of considering comorbid conditions when investigating the neurophysiological mechanisms underlying ADHD, as these conditions may substantially influence the neurophysiological profile of affected individuals and are essential for a comprehensive understanding of patient-specific neurophysiological alterations

Disclosures: W. Herrera-Morales: None. **J.V. Reyes -Lopez:** None. **L. Nuñez-Jaramillo:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.25/LL4

Topic: I.05. Working Memory

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Title: A Preliminary Investigation of Methylphenidate-Associated Neural Changes During Response Inhibition in Adults with ADHD

Authors: *D. SMITH[1], R. WISEMAN[2], R. FINDLING[4], P. BARKER[5], B. S. SLUSHER[6], G. S. SMITH[3], K. S. ROSCH[1], K. BIGOS[7];
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Abstract: Impaired response inhibition is a core feature of ADHD, manifesting as a heightened failure to withhold responses during stop-signal and Go/No-Go tasks. Neuroimaging studies attribute these deficits to several frontoparietal regions, including the right pre-supplementary motor area (pre-SMA) for motor planning, the anterior cingulate cortex for monitoring task accuracy, and the right inferior frontal cortex for suppressing motor responses. Methylphenidate (MPH) is a common ADHD treatment, yet multimodal imaging has rarely been used to characterize its specific effects on this circuitry. To identify preliminary neural correlates associated with MPH administration, 15 adults (age range: 18-38) with ADHD (11 female) completed a double-blind, placebo-controlled fMRI pilot study, yielding a final sample of 13 placebo and 12 MPH sessions. During a simple Go/No-Go task, participants responded to green spaceship stimuli (Go) and withheld responses to red stimuli (No-Go). As the across-session one-sample No-Go>Go map was null, we used a literature-derived right pre-SMA seed (MNI; 4, 14, 50; 5-mm sphere) for generalized psychophysiological interaction analyses (gPPI; PPI No-Go>PPI Go). MPH and placebo effects were compared with cluster-corrected (voxelwise $p<.001$, cluster $p<.05$) group linear mixed-effects models in AFNI's 3dLMEr. In parallel, 7T MRS quantified glutamate-to-total-creatine ratios (Glu/tCr) in the dorsolateral prefrontal and parietal cortices, and exploratory models tested whether drug condition moderated associations among task performance and Glu/tCr. Relative to placebo, MPH produced greater NoGo>Go activation in the left pars opercularis (-46, 16, 2; Z=8.4) and the right superior frontal/anterior cingulate cortex (12, 40, 28; Z=7.1), whereas placebo produced greater activation in the right hippocampus and left cerebellum. In the gPPI analysis, MPH increased right pre-SMA connectivity with the right frontoparietal network (superior frontal, superior parietal, paracentral) and the right superior temporal gyrus, whereas placebo increased right pre-SMA-right cerebellum connectivity. Activation and connectivity were not associated with DLPFC and parietal Glu/tCr nor were they associated with No-Go task performance due to ceiling effects. Together, these findings indicate that MPH shifts activation and connectivity across a distributed inhibition network spanning the left pars opercularis, dorsomedial PFC, and pre-SMA-frontoparietal circuits. Although preliminary, these spatially specific effects highlight candidate biomarkers for studies of the neurobiological mechanisms underlying MPH response.

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Viatris, Xenon. F. Consulting Fees (e.g., advisory boards); Abbvie, Ajna, Akili, Aluco, Bioprojet, BioXcel, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, Iqvia, Karuna, Lundbeck, Maplight, Merck, MJH Life Sciences, Novartis, Otsuka, PaxMedica, PCORI, Pfizer, Radius, Signant Health, Sumitomo Pharma, Sunovion, Supernus Pharmaceuticals, Takeda, Tris, Viatris, Xenon. Other; Elsevier, NIH, Oxford University Press, Sage, American Psychiatric Press, American Academy of Child & Adolescent Psychiatry. **P. Barker:** None. **B.S. Slusher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dracen Pharmaceuticals, FolHio Pharma, Samata Therapeutics, Inventor on patents covering novel GCPII inhibitor compositions and their utility. **G.S. Smith:** None. **K.S. Rosch:** None. **K. Bigos:** A. Employment/Salary (full or part-time):; Bullfrog AI, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bullfrog AI, Inc.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.26/LL5

Topic: I.04. Executive Functions

Support: International Center for Responsible Gaming

Title: A novel automated set shifting task to probe the role of serotonin in cognitive flexibility

Authors: *Y. A. PENA[1], M. G. SPRING[2], K. M. NAUTIYAL[3];
[2]Psychology and Brain Sci., [3]Neurosci., [1]Dartmouth Col., Hanover, NH

Abstract: Cognitive inflexibility is a transdiagnostic symptom found in a number of psychiatric disorders. In humans, it is often assessed using the Wisconsin Card Sorting Task (WCST). In preclinical studies, the manual attentional set shift task is most commonly used to assess cognitive flexibility, but it lacks important features for certain neural questions. To address these deficits, we developed a novel automated rule shifting task that follows a symmetric design, allows for collection of hundreds of trials per session (enabling computational modeling), and has discrete trials (allowing for alignment with recordings of neural activity). Using operant touchscreen chambers (Bussey-Saksida, Lafayette Instruments), we trained animals to seek reward by responding to multiple stimuli. The rules governing “correct” responding varied along two dimensions with two levels each: Image (e.g. plane correct vs. spider correct) and Side (Left side correct, Right side correct). Animals were trained on all four rules in individual sessions before being tested in a flexibility session, in which the active rule changed after an animal completed 5 consecutively correct responses. This task allowed us to study the outcomes of various serotonergic manipulations on cognitive flexibility. We first assessed the post-acute effects of psilocybin (3mg/kg) in C57BL/6 mice (N=12, 6M, 6F). We found that, regardless of sex, animals showed significantly increased average accuracy 24hrs after psilocybin treatment compared to saline. We then assessed the involvement of the 5-HT 1B receptor (5-HT1BR) in

the same task. We found that while 5-HT1BR knockouts had increased task engagement, they exhibited significantly impaired error monitoring evidenced across several metrics. In follow-up sessions, we tested the animals' ability to generalize image rules by changing the image pair presented in two final sessions. By all metrics, animals behaved equally well using the same rule with novel images. Ongoing work includes analyzing task-evoked c-fos expression, measuring serotonin release in the dorsomedial striatum during flexible behavior using the GRAB-5-HT sensor, and examining the effects of chronic corticosterone on task performance. These findings will clarify the role and influence of serotonin, the 5-HT 1B receptor, stress, and novel treatments in/on cognitive flexibility. This assay will hopefully serve as a translational tool for preclinical psychiatric drug development and contribute towards a richer behavioral and neural understanding of dysregulation of reward-related behaviors.

Disclosures: Y.A. Pena: None. **M.G. Spring:** None. **K.M. Nautiyal:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.27/LL6

Topic: I.04. Executive Functions

Title: Wheel running increases impulsivity in rodents

Authors: *D. R. SARUBIN[1], Q. MARINO[1], A. PRIETO[1], G. SCHNEIDER[1], A. T. BROCKETT[2,1];
[1]Biol. Sci., Univ. of New Hampshire, Newmarket, NH; [2]Psychology, Rollins Col., Clermont, FL

Abstract: Inhibitory control, the ability to stop and alter one's ongoing actions in response to immediate environmental stimuli, is vital for survival and mental health. Voluntary exercise, often operationalized as wheel running in rodents, is thought to confer positive mental health outcomes (Greenwood et al., 2011). However, the mechanistic nature of this pathway is not yet understood. In this study, we sought to determine whether wheel running affects inhibitory control in rodents and whether inhibitory control may serve as a mediator between running and mental health. To measure inhibitory control, we used the stop-change task, in which rats respond quickly to a spatial cue on 80% of trials (GO trials) and must stop and redirect planned movement on 20% of trials (STOP trials). Running rats performed similarly on GO trials but significantly worse on STOP trials relative to sedentary controls. Two possible explanations for this difference are that the runners were displaying increased impulsivity or a different reward strategy that focused on responding to common GO trials rather than uncommon STOP trials. To explore the latter possibility, we conducted a follow-up study in which 20% of the trials were GO trials and 80% were STOP trials, meaning the STOP trials became normative and the GO trials required additional cognition. If the runners displayed similar STOP trial performance but worsened GO trial performance, this would suggest that they were employing a novel reward strategy, focusing their efforts on the most common trial type. In this novel configuration of the

stop-change task, the number of GO and STOP trials that subjects completed successfully did not differ significantly between runners and sedentary rats. This suggests that the worse performance on STOP trials in the initial stop-change task might indicate increased impulsivity in runners, rather than a change in reward strategy. Future research might investigate whether running alters brain areas previously shown to be critical for STOP trial performance, such as the anterior cingulate cortex (Brockett et al., 2020; Brockett & Roesch, 2021).

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Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.28/LL7

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Operant Learning in Different Mouse Models - A Novel Touchscreen Based Analysis

Authors: *Y. DAS[1], K. STANGIS[3], G. G. MURPHY[2];
[2]MNI/MIP, [1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [3]MNI, Univ. of Michigan, MNI, Ann Arbor, MI

Abstract: Physiological differences observed in animal models are only as meaningful as the behavioral paradigms used to reveal them. Classical learning paradigms like fear conditioning and water maze, despite their foundational contributions, are limited by their reliance on aversive stimuli and challenges in translational relevance across species. Operant touchscreen-based testing offers a promising alternative: it reduces confounding factors and aligns more closely with human cognitive assessments. The Bussey-Saksida touchscreen system, developed in parallel with the Cambridge Neuropsychological Test Automated Battery (CANTAB), provides a platform for assessing cognitive impairments in neuropsychiatric and neurodevelopmental disorders such as schizophrenia and Alzheimer's disease. Touchscreens require food restriction as a motivating operant and present ways to employ a cohort of mice in multiple different learning tasks that hold independent physiological relevance. To test the validity of such results, we trained one cohort of wild-type C57BL/6NTac, and B6C3H/F1 hybrid mice and another of C57BL/6NTac, and the L-Type voltage gated calcium channel Cav1.3 knockout mice in two different working memory and procedural learning tasks - namely, Location Discrimination (LD) and Pairwise Visual Discrimination (PD). Following behavioral training, we conducted hippocampal analyses of adult neurogenesis and synaptic plasticity markers. Immunohistochemistry for Ki67 and doublecortin (DCX) quantifying proliferating progenitors and immature neurons compared between different mouse strains. Our output sustained a rich source of continuous data that was used to assess the heterogeneity in behavioral motivation as well as learning outcomes, but traditional statistical measures failed to characterize the genotypic and individual performance differences. We employed an approach based on reinforcement

learning to model the effects of context and reward in lieu of trial-history that determined latent behavioral states by fitting a hidden Markov model with Bernoulli generalized linear model observations (GLM HMM). The results suggested that the Cav1.3 knockout mice had an inverse cue following phenotype, leading to difficulties in training acquisition. Our findings highlight the importance of controlling for motivation and strain-based variables and establish a framework for linking behavioral outcomes to neurobiological markers in a reproducible and translational model of hippocampal learning.

Disclosures: Y. Das: None. **K. Stangis:** None. **G.G. Murphy:** None.

Poster

PSTR331: Inhibitory Control and Executive Dysfunction

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR331.29/LL8

Topic: I.04. Executive Functions

Support: Drake University startup funds to EE

Title: Behavioral consequences of exogenous 17B-Estradiol following repetitive mTBI in male mice

Authors: *E. EMMONS;
Drake Univ., Des Moines, IA

Abstract: Mild traumatic brain injury (mTBI) is the most common form of neurotrauma, frequently occurring in contact sports, vehicle accidents, combat, and falls. While typically associated with transient cognitive impairments and neuroinflammation, repetitive mTBI (rmTBI) can lead to chronic traumatic encephalopathy in humans, characterized by deficits in working memory, attention, and behavioral regulation. The underlying mechanisms of this cognitive impairment remain poorly understood. Utilizing a weight-drop model of single incident mTBI, past work from our lab has established that male mice display more pronounced cognitive dysfunction than female mice. When paired with complicated findings in the literature, these results suggest a possible neuroprotective role of female sex hormones. To inform future therapeutic approaches, we investigated the consequences of 17-β; Estradiol (E2) following rmTBI on various aspects of basic cognition in male mice (48 C57BL/6 mice). We assessed cognition through a rewarded T-maze, elevated plus maze, and a novel object recognition task. Our analysis suggests that E2 improved task retention in the rewarded T-maze regardless of rmTBI treatment. E2 also mitigated the anxiety-like behavior seen in the rmTBI group on the elevated plus maze. There were no consistent effects of E2 or rmTBI treatment on performance in the novel object recognition task. Ongoing work is seeking to quantify the extent of this potential mitigation of rmTBI impact at a cellular and molecular level through immunohistochemical and stereological analysis of NeuN, Iba1, GFAP, and phosphorylated tau proteins. We are also exploring the interaction between E2 and rmTBI on a modified version of

the Barnes maze that, in addition to spatial working memory, assesses executive functions such as perseveration and behavioral flexibility.

Disclosures: E. Emmons: None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.01/LL9

Topic: I.05. Working Memory

Support: The Intellectual and Developmental Disabilities Research Center
5P50HD105352-05
Cystinosis Research Network
Cystinosis Research Foundation

Title: Understanding Working Memory in Individuals with Cystinosis

Authors: *S. NANDI[1], C. BRITTENHAM[2], T. VANNEAU[2], J. J. FOXE[3], S. MOLHOLM[2]; [1]Dept. of Neurosci., [2]Departments of Pediatrics and Neurosci., Albert Einstein Col. of Med., Bronx, NY; [3]Dept. of Neurosci., Univ. of Rochester, Rochester, NY

Abstract: Advances in treatment of cystinosis, a rare autosomal recessive lysosomal storage disorder arising from mutation of the *CTNS* gene, have significantly extended life expectancy, but have also revealed neurological and cognitive sequelae. Patients report mental fog, exhaustion, and lower academic performance despite strong efforts. IQ testing reveals issues in executive function, particularly working memory, as well as difficulties with visuo-spatial skills despite conserved verbal skills. To investigate potential neural processes underlying poorer working memory performance in cystinosis, we used high-density electroencephalography (EEG) to record brain activity in participants utilizing working memory under nonverbal (visual-spatial) and verbal (visual and auditory) task demands. 38 individuals with cystinosis (ages 8-38, 28 women) and 47 typically-developing individuals (ages 8-43, 32 women) participated in neuropsychological testing and performed three working memory *n*-back paradigms (auditory verbal, visual verbal, and visual spatial) while EEG was recorded. Neuropsychological testing was consistent with prior work, revealing that while verbal IQ in cystinosis was similar to an age-matched control group, nonverbal IQ was significantly lower, as were verbal and nonverbal working memory measures. Across all three paradigms, the cystinosis group had poorer task performance, with fewer hits and a higher rate of false alarms and misses. Brainwaves corresponding to correct stimulus categorization (early P3b), working memory updating (late P3b), and consolidation/preparation (late slow wave) were significantly larger in amplitude in the cystinosis group, with group differences most apparent starting at ~300 ms. Overall, individuals with cystinosis exhibited lower performance across all three working memory tasks, accompanied by larger-amplitude cognitive brain responses. Interestingly, our findings don't

support disproportionate impairment in the visual-spatial condition as might be expected based on performance on neurocognitive assessments. Larger brain responses may reflect additional neural recruitment to complete tasks due to cystinosis-induced oxidative stress and mitochondrial dysfunction.

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Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.02/LL10

Topic: I.05. Working Memory

Support: dtec.bw/MEXT (European Union - NextGenerationEU)
University of the Bundeswehr Munich

Title: Examining the effects of theta-burst stimulation on dorsolateral prefrontal cortex modulation, and working memory performance using a controllable pulse waveform.

Authors: *D. AGBOADA, R. RETHWILM, W. SEIBERL, W. MACK;
Univ. of the Bundeswehr Munich, Neubiberg, Germany

Abstract: Working memory (WM) is a critical cognitive function that supports everyday activities and is particularly vulnerable to age-related decline. The reduction or loss of WM function is prevalent in many neuropsychiatric disorders such as Alzheimer's disease. Theta-burst stimulation (TBS) has been investigated as a promising approach for enhancing WM performance. However, there is little consensus regarding which TBS protocols improve WM in healthy individuals. This might be due to the modulation of WM performance with TBS protocols from suboptimal pulse waveform parameters of conventional TMS devices. We investigated the effects intermittent (iTBS), and continuous (cTBS) theta-burst stimulation compared with sham on cortical excitability and WM performance using a controllable pulse parameter transcranial magnetic stimulator (cTMS). Three participants completed three stimulation sessions in a randomized crossover design, receiving either iTBS, cTBS, or sham stimulation (data collection is currently ongoing, and n = 15 sample size is planned). Each session was separated by a minimum of one week. Resting motor threshold (RMT) was determined in the primary motor cortex, and 75 % RMT was used for the TBS intervention. Participants' baseline cortical excitability was measured using single-pulse cTMS-EEG (80 TMS-evoked potentials recorded with 100% RMT) at F3 electrode position (10-10 EEG system), followed by assessment of WM using the running-span task (RST). After baseline measurements, one of the three conditions of TBS was applied. Immediately after stimulation, cortical excitability and WM were reassessed. Global mean field power (GMFP) was used as an index of cortical reactivity, while the averaged correct response was used to quantify WM

performance. Preliminary analyses did show sham stimulation did not induce any significant changes between cortical excitability before and after stimulation, nor were there any differences in baseline and post-stimulation averaged correct response on the RST. Compared to sham, both conditions of TBS showed significant changes in cortical excitability. For the iTBS protocol, enhancements in GMFP were observed within the first 60 milliseconds, as well as 200-300 ms post-stimulation, but no corresponding changes in pre- and post-measurements of RST averaged correct response observed. The cTBS protocol produced expected reductions in GMFP. These changes were accompanied by a reduction in averaged correct response on the RST relative to baseline. In conclusion, both TBS protocols modulated prefrontal cortical excitability; however, only cTBS produced corresponding behavioural changes in WM performance.

Disclosures: D. Agboada: None. **R. Rethwilm:** None. **W. Seiberl:** None. **W. Mack:** None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.03/LL11

Topic: I.05. Working Memory

Support: F32MH124268

Title: Cerebellar perturbation impairs human working memory and degrades spatial tuning throughout cortex

Authors: *J. A. BRISSENDEN[1], M. VESIA[2], T. G. LEE[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Working memory, the transient maintenance and manipulation of information, is fundamental to human cognition. While working memory is typically thought to rely on frontoparietal cortex, recent evidence suggests the cerebellum may contribute to a host of cognitive functions, including memory. It is currently unknown whether cerebellar processing is causally necessary for the persistent maintenance of visual information and whether spatially tuned cortical activity is dependent on intact cerebellar function. We combined functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) of frontal, parietal, and cerebellar cortex in humans. We show that cerebellar perturbation broadly degrades cortical spatial tuning and impairs spatial working memory recall. This impairment matches that observed following perturbation of canonical frontoparietal working memory areas. These findings establish a causal role for the cerebellum in the persistent maintenance of cognitive representations, necessitating a revision of prevailing accounts of human working memory.

Disclosures: J.A. Brissenden: None. **M. Vesia:** None. **T.G. Lee:** None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.04/LL12

Topic: I.05. Working Memory

Support: PASRES BR009

Title: Adaptive digital learning modulates encoding and retrieval dynamics in visuospatial working memory of primary school children: An EEG study

Authors: *Y. OUATTARA;
Biosci., UNIVERSITE FELIX HOUPHOUËT-BOIGNY, Abidjan, Côte D'Ivoire

Abstract: Adaptive digital learning shows promise in customizing education, yet its precise impact on the neural dynamics underlying visuospatial working memory (VSWM) in children remains underrepresented. This study investigated how adaptive versus standard trial-delivery formats modulate brain activity during memory encoding and retrieval. Continuous EEG activity was recorded using a wireless 14-channel Emotiv EPOC X headset from primary school students during a digital Corsi Block-Tapping task under two conditions: a Standard condition with fixed sequence lengths and an Adaptive condition adjusting difficulty in real-time based on performance. Topographical spectral analysis focused on frontal Theta (4-8 Hz) and posterior Alpha (8-12 Hz) oscillations. Event-based analyses separated encoding and retrieval epochs using behavioral markers extracted from the task structure. The results revealed that the Adaptive condition induced a powerful spatio-temporal modulation of neural networks. During encoding, the Adaptive format elicited a strong synchronization of Theta power over posterior regions, reflecting heightened sensory-cognitive processing required to register complex spatial sequences. Strikingly, upon transitioning to the retrieval phase, this activation shifted radically toward prefrontal and frontal networks (AF3, F3, F4, AF4), signaling a massive recruitment of executive control and decision-making resources. In contrast, the Standard condition exhibited static, diffuse, and unspecialized Theta activity across both phases. Furthermore, posterior Alpha power was strongly attenuated (desynchronized) throughout the Adaptive task, particularly during retrieval, indicating sustained cortical activation and enhanced attentional engagement, whereas the Standard condition showed persistent Alpha synchronization associated with cognitive under-stimulation and attentional dropout. These findings demonstrate that adaptive digital interfaces do not merely reduce cognitive load; rather, they actively reshape the encoding and retrieval dynamics of VSWM. By dynamically sustaining optimal challenge levels, adaptive learning prevents disengagement and optimizes fronto-posterior network orchestration, offering critical neuroscientific insights for child-centered educational technologies.

Disclosures: Y. Ouattara: None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.05/LL13

Topic: I.05. Working Memory

Support: MSCA-PF-GF 101146138

Title: Causal evidence for different priority states of visual working memory representations in the primary visual cortex: A combined TMS-EEG study

Authors: *P. PHYLACTOU[1], E. F. ESTER[1], N. KONSTANTINOU[2];
[1]Psychology, Univ. of Nevada, Reno, Reno, NV; [2]Cyprus Univ. of Technol., Limassol, Cyprus

Abstract: Visual working memory (VWM) enables the short-term maintenance of visual information to guide behavior. According to the sensory recruitment framework, elemental visual features (e.g., orientations) are maintained in the primary visual cortex. Because not all items held in VWM are simultaneously relevant for behavior, mechanisms of selective attention are needed to prioritize subsets of stored items needed to meet immediate goals. Prior work has demonstrated that priority allocation produces distinct maintenance states: prioritized items can be decoded from neuroimaging signals, whereas unprioritized items cannot (unless subsequently reprioritized). Whether priority-driven divergence in maintenance states extends to primary visual cortex is unknown. Here, we report preliminary evidence that it does. Using transcranial magnetic stimulation (TMS), which produces dissociable effects on prioritized vs. unprioritized maintenance states in frontoparietal cortex, we tested 25 participants on a VWM task with occipital TMS. Relative to sham TMS, occipital TMS increased accuracy for prioritized items while decreasing accuracy for unprioritized items. EEG decoding mirrored this pattern: occipital TMS enhanced decoding of prioritized items, yet reduced decoding of unprioritized items during reprioritization attempts. Together, these findings provide causal evidence that prioritization drives distinct VWM maintenance states in primary visual cortex. We interpret the direction of the TMS effects as reflecting interference with storage processes supporting unprioritized items: by disrupting those representations, TMS frees resources that benefit prioritized item processing and impairs the reprioritization of unprioritized ones. These results inform ongoing debates about the role of primary visual cortex in VWM storage.

Disclosures: P. Phylactou: None. **E.F. Ester:** None. **N. Konstantinou:** None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

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Program #/Poster #: PSTR332.06/LL14

Topic: I.05. Working Memory

Support: NIH Grant MH103790

Title: Dynamic Reconfiguration of Working Memory Networks in Youth at Familial Risk for Schizophrenia

Authors: *A. WINN[1], A. BELGER[2];
[1]UNC Chapel Hill, Chapel Hill, NC; [2]Univ. of North Carolina, Chapel Hill, NC.

Abstract: DRAFT SFN ABSTRACT
Working memory (WM) supports goal-directed behavior through coordinated engagement of large-scale executive brain networks, which must continually balance stability of task focus with flexibility of network reconfiguration in response to cognitive demands. Schizophrenia and related psychopathologies are marked by robust WM impairments, yet the dynamic neural mechanisms underlying these deficits in youth remain poorly understood. Here, we examine task-positive network flexibility (TPNF)—the moment-to-moment reorganization of functional connectivity—as a biomarker of cognitive vulnerability in adolescents at familial risk for psychosis.
One hundred sixty-seven adolescents (ages 9–18) from a longitudinal neurodevelopmental cohort completed an n-back WM task with graded load (0-back to 2-back) during fMRI. Participants were classified as familial high-risk (FR+; first-degree relative with schizophrenia) or low-risk (FR−; no such history). Preprocessed surface-based time series from 200 cortical parcels were used to compute sliding-window functional connectivity, and Louvain modularity was applied within each window to detect communities. Regional flexibility was defined as the proportion of times each parcel changed community allegiance across consecutive windows and was averaged within the seven canonical Yeo networks.
Across participants and loads, flexibility was highest in Default Mode (0.821) and Frontoparietal Control (0.820) networks, intermediate in Salience/Ventral Attention (0.741) and Visual (0.732) networks, and lowest in Dorsal Attention (0.697), Somatomotor (0.659), and Limbic (0.706) networks. This hierarchy aligns with known functional gradients, with associative control and default systems showing the greatest large-scale reconfiguration during WM demands.
These findings demonstrate the feasibility and reliability of estimating network-level flexibility from surface-based sliding-window analyses in youth and suggest that task-positive networks exhibit robust dynamic coupling under increasing cognitive load. Ongoing work will test how TPNF is modulated by load and familial risk status and whether flexibility signatures predict behavioral performance and clinical outcomes, with the goal of
identifying early biomarkers of cognitive resilience and vulnerability in emerging psychopathology.

Disclosures: A. Winn: None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.07/LL15

Topic: I.05. Working Memory

Title: Emotional Context Outweighs Cognitive Demand in Organizing Brain Body Physiology

Authors: *A. RANJAN[1], M. MEGJHANI[2];
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Abstract: Brain-body physiological coupling during working memory is rarely examined as a dynamic structure as most studies ask whether individual signals change with load, not whether the coupling architecture reorganizes with context.We conducted a secondary analysis of a publicly available multimodal dataset (Khazaei et al., 2025, PhysioNet) collected during n-back working memory (WM) tasks under calming and vexing music (emotional context). Available signals included functional near-infrared spectroscopy (fNIRS), electrodermal activity (EDA), electrocardiography (ECG), and skin temperature (SKT). We extracted block-level prefrontal oxygenated hemoglobin (HbO), heart rate variability (RMSSD), tonic/phasic EDA, and SKT. We computed a Brain-Body Coupling Index (BBCI), 6-dimensional coupling vectors, a Coupling Stability Index, and shift-vector analyses per subject-by-condition. An Autonomic Stress Index (ASI; 7 autonomic measures) was related to HbO via repeated-measures correlation. Condition effects on BBCI were tested using a linear mixed-effects model and 2×2 repeated-measures ANOVA.A total of 5 adults (3F/2M) were included, contributing 160 blocks across a 2×2 design (1-back/3-back × calming/vexing music; 32 blocks/subject; 8 per condition; n=155 for prediction analyses). BBCI showed no significant condition effect (all $p>0.55$). Within-subject coupling variance exceeded between-subject variance 6.6-fold (1.160 vs. 0.176). Music shifted 6-D coupling vectors more than cognitive load (1.33 vs. 0.81; 5/5 subjects; 67-73% directional agreement). Autonomic coherence (mean $|r|=0.445$) exceeded brain-autonomic coupling ($|r|=0.324$; $t(4)=2.50$, $p=0.067$, $d=2.08$; rank-biserial $r=+0.87$). ASI correlated with whole-head HbO (rmcorr $r=+0.205$, $p=0.010$) but not Prefrontal Cortex-specific channels ($r=+0.120$, $p=0.136$); strongest under Calm-3back ($r=+0.319$, $p=0.045$), near-zero under both exciting-music conditions.Emotional context reorganized physiological coupling more powerfully than cognitive demand, in other words, the music someone listens to changed how their brain and body coordinated more than the difficulty of the task they were doing. The body's autonomic systems coupled more tightly with each other than with the brain, suggesting the brain is not the dominant hub in this network. Single-number coupling summaries missed these effects entirely; only vector-level analysis revealed them. These findings suggest physiological biomarkers of cognitive load may be capturing emotional state instead, and that music could be used to actively regulate brain-body state and improve cognitive performance in real time.

Disclosures: A. Ranjan: None. **M. Megjhani:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American Heart Association Project Nr.: 24SCEFIA1259295.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.08/LL16

Topic: I.05. Working Memory

Support: NIH NIA 5R01AG090302
NIH 1S10OD034414

Title: Interictal Epileptiform Discharges Transiently Impair Working Memory Performance in Stereo-EEG Monitored Epilepsy Patients

Authors: *S. SHERZAI[1,2,3], J. ZOU[4,2], A. C. PAULK[2], T. AVIGDOR[2], P. HADAR[2], S. S. CASH[2], J. D. ROLSTON[3], R. ZELMANN[2];
[1]Neurosurg., Mass Gen. Brigham, Boston, MA; [2]Neurol., Massachusetts Gen. Hosp., Boston, MA; [3]Neurosurg., Brigham and Women's Hosp., Boston, MA; [4]MIT, Cambridge, MA

Abstract: Interictal epileptiform discharges (IEDs) are brief, electrical events that occur between seizures in patients with epilepsy and are hypothesized to transiently disrupt cognitive processing. While prior work has demonstrated IED-associated cognitive impairment in scalp EEG cohorts, the spatial specificity of this effect in human intracranial recordings remains poorly characterized. We examined whether IEDs detected during stimulus encoding predict trial-level working memory accuracy in three drug-resistant epilepsy patients undergoing stereoelectroencephalography (sEEG) monitoring. Three patients completed an n-back working memory task (Load 1: 1-back, Load 2: 2-back) while broadband sEEG was recorded across 132-197 channels per patient. IEDs were detected using the automated Janca et al. (2015) spike detector (10-60 Hz bandpass, k1=3.65) applied to each channel independently. For each trial, IED presence was defined as one or more detections within a 1-second post-stimulus window, capturing the encoding period. Accuracy was compared between IED-present and IED-absent trials using the Mann-Whitney U test with Cliff's Delta effect size, stratified by cognitive load. Across all electrodes pooled across the patients, IED-present trials showed lower Load 2 accuracy compared to IED-absent trials (78.2% vs. 84.5%, Δ=−6.3%, Cliff's Delta=−0.063, MWU p=0.239). Region-of-interest analyses targeting mesial temporal, superior temporal, and orbitofrontal cortex revealed an effect specifically in orbitofrontal cortex: IED-present trials were associated with markedly lower accuracy compared to IED-absent trials at Load 1 (82.9% vs. 93.6%, Δ=−10.7%, Cliff's Delta=−0.107, MWU p=0.003). A trend in the same direction was observed at Load 2 (72.7% vs. 80.8%, Δ=−8.1%, Cliff's Delta=−0.081, MWU p=0.140). No significant effects were observed in mesial or superior temporal regions. Response time did not differ between IED-present and IED-absent trials, suggesting IEDs specifically impair memory encoding rather than motor output or general attention. These findings suggest that orbitofrontal IEDs during stimulus encoding predict working memory errors in sEEG patients, highlighting the orbitofrontal cortex as a critical node in the IED-cognition relationship and motivating a larger-scale investigation.

Disclosures: S. Sherzai: None. **J. Zou:** None. **A.C. Paulk:** None. **T. Avigdor:** None. **P. Hadar:** None. **S.S. Cash:** None. **J.D. Rolston:** None. **R. Zelmann:** None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.09/LL17

Topic: I.05. Working Memory

Support: NIH R01 AG053952
NIH R35 AG072307

Title: Anterior Cingulate Cortex Subregional Volumes and Domain-Level Cognitive Performance in Cognitively Unimpaired Older Adults

Authors: *M. A. VILLARROEL[1], C. MOLINA-HIDALGO[3], H. HUANG[3], L. WAN[3], G. GROVE[4], C. URDANETA[3], S. JAIN[2], P. SOLIS-URRA[6], B. SUTTON[7], E. D. VIDONI[8], J. M. BURNS[9], C. HILLMAN[10], A. F. KRAMER[11], E. MCAULEY[12], C. KANG[5], L. E. OBERLIN[2], K. I. ERICKSON[2];
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Abstract: BACKGROUND: The anterior cingulate cortex (ACC) is structurally and functionally heterogeneous, with roles in cognitive control and adaptive behavior. While cingulate morphology has been linked to cognition in aging, it is unclear whether associations are specific to the anterior midcingulate cortex (aMCC) or reflect broader ACC variation. We examined associations between ACC subregional volumes and five cognitive domains in cognitively unimpaired older adults.
METHODS: Baseline data from 641 cognitively unimpaired older adults from the IGNITE study were included. Participants underwent T1-weighted structural MRI and neuropsychological assessment. Bilateral ACC subregional volumes were derived using FreeSurfer segmentation, including anterior ACC, aMCC, mid-posterior ACC, post-dorsal ACC, post-ventral ACC, and total ACC. Linear regression models examined associations between each subregion and episodic memory, working memory, visuospatial ability, executive function/attentional control, and processing speed, adjusting for age, sex, education, site, and intracranial volume. Sensitivity models examined whether aMCC associations persisted after adjusting for non-aMCC ACC volume.
RESULTS: Greater aMCC volume was associated with better episodic memory (β=0.060, p=.017), working memory (β=0.061, p=.005), and visuospatial ability (β=0.055, p=.017). Greater post-dorsal ACC volume was associated with better working memory (β=0.060, p=.010), visuospatial ability (β=0.057, p=.019), executive function/attentional control (β=0.068, p=.008), and processing speed (β=0.060, p=.027). Total ACC volume was associated with working memory (β=0.059, p=.023) and visuospatial ability (β=0.057, p=.035). Anterior ACC, mid-posterior ACC, and post-ventral ACC showed no significant associations. In sensitivity models,

aMCC associations with episodic and working memory persisted.
CONCLUSIONS: In cognitively unimpaired older adults, ACC-cognition associations were not uniform across the ACC but were most evident in midcingulate and post-dorsal subregions. aMCC volume was associated with episodic memory, working memory, and visuospatial ability, while post-dorsal ACC showed broader associations across cognitive domains. Sensitivity analyses suggested that aMCC associations with episodic memory and working memory were not fully explained by non-aMCC ACC volume. These findings suggest that structural variation within specific ACC subregions may be differentially linked to late-life cognitive performance.

Disclosures: M.A. Villarroel: None. **C. Molina-Hidalgo:** None. **H. Huang:** None. **L. Wan:** None. **G. Grove:** None. **C. Urdaneta:** None. **S. Jain:** None. **P. Solis-Urra:** None. **B. Sutton:** None. **E.D. Vidoni:** None. **J.M. Burns:** None. **C. Hillman:** None. **A.F. Kramer:** None. **E. McAuley:** None. **C. Kang:** None. **L.E. Oberlin:** None. **K.I. Erickson:** None.

Poster

PSTR332: Distributed Mechanisms of Working Memory: Clinical and Applied

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR332.10/LL18

Topic: I.05. Working Memory

Support: Chan Zuckerberg Initiative

Title: Neuroinflammation via a short-term high-cholesterol diet disrupts excitatory and inhibitory balance and impairs working memory in larval zebrafish

Authors: *M. X. NGUYEN[1], D. ZOCCHI[3], A. LOZEVSKI[1], J. ZHANG[2], A. MILLER[1], S. YAO[1], E. YANG[4];
[1]Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Univ. of North Carolina Chapel Hill, Chapel hill, NC; [3]Arc Inst., Palo Alto, VA; [4]Biol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Excess dietary cholesterol has been strongly linked to Alzheimer's disease, vascular dementia, and age-related cognitive decline through molecular consequences, including systemic inflammation, neuroinflammation, and increased microglial and astrocytic activity. Yet, how these molecular changes alter brain-wide neural activity and network organization to produce selective cognitive failure remains unknown. To address this gap, we placed larval zebrafish in a closed-loop virtual reality environment to perform a working memory (WM) task while using whole-brain cellular-resolution light-sheet microscopy to measure neural activity across the brain enabling us to define how a high-cholesterol-diet (HCD) disrupts network dynamics during cognition. We found after short-term HCD exposure, larval zebrafish retained simple local motion processing and sensory-to-motor transformation but exhibited severe deficits in positional WM compared with normal-diet (ND) controls. Whole-brain imaging revealed that HCD disrupts WM by weakening brain-wide inhibitory tone, thereby destabilizing the persistent

neural activity that encodes memory of past position. Granger causality analysis showed that HCD fish have weaker functional connectivity and reduced inhibitory interactions among sensory input, WM, motor planning, and premotor circuits compared with ND controls. Pharmacologically treating with the anti-inflammatory drug (acetylsalicylic acid) partially restored WM in HCD fish, indicating that inflammation contributes to this cognitive deficit. In contrast, gentle optogenetic stimulation of inhibitory networks fully rescued WM impairment, demonstrating that excitatory/inhibitory (E/I) circuit imbalance is a causal driver of the WM deficit. Together, these findings provide a mechanistic link between dietary cholesterol, systemic inflammation, disrupted E/I circuit balance, and impaired WM.

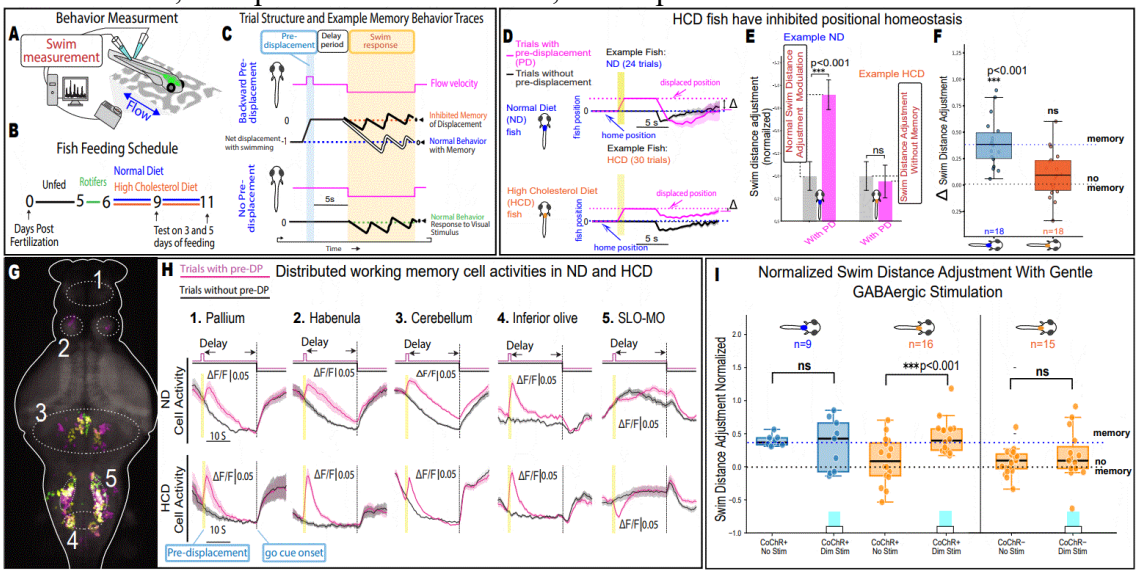


Figure Legend: A) Experimental setup. **B)** Fish feeding schedule. **C)** Experimental trial structure used to test working memory. **D)** Example fish trajectories across trials: ND fish return to home position after displacement, whereas HCD fish do not. **E)** HCD fish do not adjust swim distance based on pre-displacement history. **F)** Population data from HCD and ND fish (n = 18 fish per group) showing that HCD fish fail to use memory to adjust their swim distance to return home. **G)** Example brain-map showing regions of interest. **H)** Brain-wide cellular activity across brain regions in representative ND and HCD fish. **I)** Low-intensity stimulation of inhibitory neurons rescues HCD-induced working memory impairment in the virtual reality environment.

Disclosures: M.X. Nguyen: None. **D. Zocchi:** None. **A. Lozevski:** None. **J. Zhang:** None. **A. Miller:** None. **S. Yao:** None. **E. Yang:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.01/LL19

Topic: I.05. Working Memory

Support: Israel Science Foundation #1088/21

Title: Reconsidering Updating Costs in Working Memory: Evidence from Response Times, Pupillometry, and Meta-Control

Authors: *Y. KESSLER, M. SALOMON, N. GIL-ADI;
Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: Current models of working memory (WM) treat updating as a slow, effortful process dependent on controlled gating. Using a modified reference-back paradigm, we challenge this view. When a single item is held in WM, responses are faster and pupil diameter is smaller during updating than during maintenance, reflecting an updating benefit in both speed and mental effort. This pattern reverses when multiple items are maintained. In a second set of experiments, we manipulated the proportion of updating versus maintenance trials and found that the dominant operation in the block determined performance costs: an updating cost emerged when maintenance dominated (75% of trials), whereas an updating gain emerged when updating dominated. Together, these results argue against updating as a dedicated control process. Rather, encoding into WM emerges as a by-product of selective attention and response selection, while actively preventing updating, rather than updating itself, requires additional processing. Additionally, the default mode of WM, flexibility or stability, is determined by task context, reflecting flexible meta-control over updating and maintenance.

Disclosures: Y. Kessler: None. **M. Salomon:** None. **N. Gil-Adi:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.02/LL20

Topic: I.05. Working Memory

Title: Working memory is enhanced by domain-specific structured knowledge

Authors: *J. MILLER[1], C. GONZALEZ[2], A. HELLER[1];
[1]Psychology, [2]Chem., Univ. of Miami, Coral Gables, FL

Abstract: Working memory (WM) is critical for adaptive behavior by storing and transforming sensory information. But in comparison to long-term memory systems, WM is critically capacity-limited and sharply declines with only a few items. However, more recent evidence shows that WM precision and capacity are bolstered for familiar and meaningful items (Chung et al., 2024). Neural representations for WM content can also shift in their substrates and representational format with learning (Miller & Constantinidis, 2024). But, the mechanisms underlying interactions between WM and learning remain poorly understood. How do long-term learning and memory enhance the limited capacity of WM? Here, we leveraged the unique environment of semester-long organic chemistry courses to study how stimulus-specific and

conceptual-level knowledge of organic compounds affected their storage in WM.
Organic chemistry students (human participants) completed a novel WM task for chemical structures at three timepoints during the semester. On each trial, participants were shown a varying number (1-5 items) of organic compounds, simultaneously presented around a central fixation point. After a short delay (2s), they responded whether a probe item matched the stimulus from a randomly selected location (50% match/non-match). The stimuli consisted of bond-line drawings of 40 unique compounds varying in 4 structures (e.g., six-carbon ring or chain) and 10 functional groups (e.g., NH2, COOH, Cl). A high-level group effect of learning was found in comparison to a control group of participants (students in a psychology course). Chemistry students showed higher memory strength for organic compounds at lower WM loads (1-3), but not for higher loads (4-5), where chance-level behavior was reached.
In longitudinal testing, for all WM loads, chemistry participants' response time on correct trials was significantly faster across three sessions. Interestingly, evidence for higher-level learning effects was found in a positive relationship between WM and class performance: among chemistry students, mean exam grades correlated with WM capacity measures (Cowan's k) on the task, driven by high WM loads. Finally, as students gained expertise in the functioning and reactivity of compounds, they paradoxically performed worse over time when a lure probe matched the functional group of the original stimulus compound - suggesting an increasing influence of higher-level stimulus properties over time. In sum, this suggests enhanced memory strength, but also potential interference effects, as long-term learning and higher-order conceptual knowledge were able to be integrated into WM.

Disclosures: J. Miller: None. **C. Gonzalez:** None. **A. Heller:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.03/LL21

Topic: I.05. Working Memory

Support: STI2030-Major 38 Projects, No.2021ZD0203700/2021ZD0203705
NYU Shanghai Boost Fund

Title: Sensory-memory network with efficient and uncertainty coding accounts for working-memory errors

Authors: *H. ZHANG, X. XIE, S. LIM;
New York Univ. Shanghai, Shanghai, China

Abstract: Behavioral errors can provide a window into how the brain represents and maintains information. Here, we used errors in a delayed orientation-estimation task to ask how perceptual representations change while held in working memory (WM). Two well-established signatures - repulsive bias away from cardinal axes and enhanced precision near cardinal orientations - have

traditionally been attributed to sensory efficient coding under the Bayesian observer framework. However, recent experiments suggest these errors continuously evolve during WM, posing a challenge that neither static sensory models nor traditional WM models can address. Further, their magnitudes scale with stimulus uncertainty; yet this dependence lacks a dynamic and mechanistic explanation.

We propose a unified framework that combines efficient sensory coding with top-down WM feedback. In a network implementation, a heterogeneously tuned sensory population interacts bidirectionally with a ring-attractor memory population. Through this interaction, the network behaves like a discrete attractor model with a relatively shallow energy landscape and an anisotropic noise. The model reproduces delay-dependent behavior errors while preserving characteristic perceptual error patterns.

Critically, this framework also explains why stimulus uncertainty modulates these error patterns. Using low-dimensional analyses and RNN training-based parameter searches, we found that the behavioral effects of stimulus uncertainty are captured when memory-to-sensory feedback is overall inhibitory and when the memory network encodes uncertainty. In this regime, more uncertain stimuli evoke weaker memory activity, reducing inhibitory feedback to sensory areas and increasing the influence of sensory heterogeneity. This, in turn, amplifies repulsive biases and alters the pattern of response variability.

Overall, our framework provides a single mechanistic account linking efficient sensory coding, working-memory dynamics, uncertainty representation, and feedback inhibition. It suggests that behavioral errors in delayed estimation tasks emerge from interactions between sensory and memory circuits, explaining how these errors vary with delay duration and stimulus uncertainty across diverse experimental conditions.

Disclosures: H. Zhang: None. **X. Xie:** None. **S. Lim:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.04/LL22

Topic: I.05. Working Memory

Support: NSF Grant PHY-2309135
Gordon and Betty Moore Foundation Grant No. 2919.02
Kavli Institute for Theoretical Physics (KITP)

Title: Low-dimensional Neural Codes Suppress Neuronal Noise and Extend the Working Memory Duration

Authors: *M. PAPILLON[1], F. DINC[2], C. FENG[3], M. BLANCO-POZO[4], I. D. LANDAU[5], M. J. SCHNITZER[6], P. YUAN[3], N. MIOLANE[1];
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United Kingdom; [5]Applied Physics and Biol., Stanford Univ., Stanford, CA; [6]Depts. Biol. & Applied Physics, Stanford University, HHMI, Stanford, CA

Abstract: Neurons are noisy computational substrates, yet large neural populations achieve reliable computation. What determines the maximal duration that a noisy population can sustain working memory? We study this question with recurrent networks subject to stochastic noise and present three theoretical results. First, networks suppress independent neuronal noise when activity lies on a low-dimensional latent manifold. Second, this structure induces correlated noise across neurons, limiting the downstream information that can be extracted. Third, these effects yield an analytical bound on working memory duration that scales linearly with network size. We test these predictions using large-scale neocortical recordings, and provide a behavioral signature in mice consistent with the theory. Overall, noise suppression constitutes a key functional benefit of low-dimensional neural coding, with which large populations sustain reliable working memory over extended timescales.

Disclosures: M. Papillon: None. **F. Dinc:** None. **C. Feng:** None. **M. Blanco-Pozo:** None. **I.D. Landau:** None. **M.J. Schnitzer:** None. **P. Yuan:** None. **N. Miolane:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.05/Web Only

Topic: I.05. Working Memory

Support: John Carroll University Funding

Title: Kratom, Working Memory, and Side Effects in Rats

Authors: *C. H. WIDEMAN[1], H. M. MURPHY[2];
[1]Dept. of Biol., [2]Dept. of Psychology, John Carroll Univ., University Heights, OH

Abstract: Kratom (Mitreagyna speciose) is a plant that is indigenous to a region of Southeast Asia and has been used to manage painful demands of physical labor, enhance mood and well-being, and as a substitute for opioids. While kratom use or sale has been banned or restricted in several countries, kratom products are currently legal and accessible online and in stores in many areas of the United States. The U.S. Drug Enforcement Administration has listed kratom as a "drug of concern". The current study examined the effects of kratom powder on working memory and side effects of the drug in rats. Utilizing control and experimental rats, the study was divided into two periods: 1) habituation and 2) experimental. During the experimental period kratom was orally administered to the experimental animals in a chocolate Ensure treat. Spatial working memory was tested utilizing the Morris water maze involving two components: a) the trial run in which the rat discovered the location of a platform and b) the test run in which the animal recalled the location of the platform. Gross motor activity of animals was determined from analysis of revolutions of running wheels located in the home cages of the animals.

Metabolic parameters of food and water intake and renal adiposity were also recorded. It was hypothesized that, compared to control rats, kratom-treated animals would have impaired working memory with some adverse metabolic side effects related to drug consumption. Results demonstrated that the two groups showed no significant differences in the time that it took for them to reach the platform at either the beginning or the end of the experimental period. Thus, no effect was noted in spatial learning with the drug. Motor activity in the experimental group was significantly lower than that of the control group; thus, noted lethargy of the experimental animals may have developed with the use of the drug related to an effect on muscle action. Renal fat in the experimental group was significantly higher than in the control group possibly indicating a metabolic effect of the drug. Water intake of the experimental group was significantly lower than the control group which may have occurred because of dehydration, a phenomenon frequently reported in human kratom users. Kratom dehydration could have serious consequences for good health and increase the danger of suffering serious conditions affecting muscles, skin, kidney, and the cardiovascular system. The risk of developing unintended health problems should be carefully weighed before consuming kratom.

Disclosures: C.H. Wideman: None. **H.M. Murphy:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.06/LL23

Topic: I.05. Working Memory

Title: Skin crawling, memory degrading: impaired working memory for aversive emotional content

Authors: *C. CAIL, K. TIMPANO, J. MILLER;
Psychology, Univ. of Miami, Miami, FL

Abstract: Navigating daily life requires the integration of emotional processing and regulation with “cold cognitive” systems such as working memory (Shenhav, 2024). Prior research has demonstrated altered long-term memory for fearful and disgusting stimuli compared to neutral content (Chapman et al., 2013), but how does aversive content impact our more capacity-limited working memory? We developed a novel task to test how working memory is affected by parametrically modulating the proportion of affective content. Participants completed a visual working memory task with four sequential animal images per trial, followed by a probe requiring a match/non-match decision. Stimuli across three counterbalanced, emotional categories were selected from aversive image databases of animals and scenes/objects: fear (e.g., spiders/snakes), disgust (e.g., cockroaches/centipedes), or neutral/positive (e.g., cats/butterflies). Intermixed trials systematically varied in emotional load, with 0-4 fear or disgust stimuli per trial (remaining images neutral). A second version of the task that probed working memory temporal ordering effects was also tested. Performance showed a pronounced decline in disgust trials: memory

strength (d′) decreased with a greater proportion of disgust items in memory (ratio of disgust to neutral items). In contrast, fear trials showed stable performance across fear load levels with similar performance to neutral trials. To examine whether retrieval demands contributed to this effect, we separated partial-disgust trials by stimulus and probe emotional category (partial disgust trials had either a neutral or disgust probe). Unexpectedly, neutral probe accuracy exceeded disgust probe accuracy for trials with both fewer (1 disgust / 3 neutral) and more (3 disgust / 1 neutral) disgust stimuli. This stimulus-probe interaction suggests a disproportionate and specific reduction in working memory strength for disgust stimuli. Finally, we also tested whether inter-individual variability in task performance would be related to trait-level emotional functioning. Accuracy on neutral trials strongly negatively correlated with individual-level disgust sensitivity, suggesting a lingering influence of disgust content across the task. These trait-level disgust effects in a working memory context extend findings of a "difficulty in disengagement" from disgust stimuli for disgust-sensitive individuals (Cisel et al., 2007). Altogether, these findings suggest a specific impairment in working memory for disgusting stimulus content, highlighting a unique, dynamic interaction between affective and working memory systems.

Disclosures: C. Cail: None. **K. Timpano:** None. **J. Miller:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.07/LL24

Topic: I.05. Working Memory

Support: NIA R56AG080816

Title: Sleep Disruption Outweighs Cytokine Biomarker and Sex-Hormone Impacts on Working Memory Function in Middle Aged Women

Authors: *S. L. GORNIAK[1], E. LAVOY[2], S. WOODS[3], A. HERNANDEZ[3], L. POLLONINI[4], R. MATHEW[5];
[1]Hlth. & Human Performance, [3]Psychology, [4]Engin. Technol., [2]Univ. of Houston, Houston, TX; [5]Univ. of Texas Hlth. Sci. Ctr., Houston, TX.

Abstract: Adult women of color are negatively impacted by risks and complications associated with poor sleep and elevated cytokine biomarkers, resulting in functional impairment in cognitive function. The development of cognitive impairments has also been linked to sex-hormone changes during the transition to menopause. Evaluation of these risk factors is often conducted independently, without consideration of the confluence of these factors on the development of mild cognitive impairments in midlife in women. In this study, 50 middle-aged women (age = 46 ± 9 years) who self-identified as belonging to an underrepresented group were recruited and enrolled to participate in a study on health and memory. While Montreal Cognitive

Assessment (MoCA) values were found to be in the healthy range in this sample (total score = 26 ± 3); deficits in specific domains were noted (Attention, Abstraction, Orientation, and Delayed Recall; all $p < 0.05$). Total MoCA scores and domain scores in Attention and Delayed Recall were primarily impacted by measures indicative of obstructive sleep apnea (OSA) ($p < 0.05$) while domain scores in Abstraction & Orientation were more influenced by cytokine biomarkers ($p < 0.05$). Deeper evaluation of short-term memory (working memory via N-back testing) also indicated a predominance of OSA-associated markers negatively impacting memory function ($p < 0.05$). Some influence of cytokine biomarkers (e.g., IL-10) on memory functions were found ($p < 0.05$); whereas the influence of sex-hormone levels on memory function was largely absent. The incidence of OSA (apnea hypopnea index (AHI) >= 5) as per overnight polysomnography assessment in this sample was 70.8%. These data indicate that sleep disruption, particularly sleep disruption associated with hypoxic events, predominates impaired memory function in middle aged women of color. The concurrent but lesser impact of cytokine biomarkers on memory function in middle aged women is consistent with known bi-directional relationships between cytokine biomarkers and sleep disruption. The largely absent impact of serum-based sex-hormone levels on memory function in this sample suggests that sleep disturbances predominate other potential pathways for memory impairments in during midlife in women. These data indicate that interventional work focusing on improving sleep disruption (via treatment of OSA) may provide a powerful pathway for prevention of functional cognitive impairments during midlife in women of color and beyond.

Disclosures: S.L. Gorniak: A. Employment/Salary (full or part-time):; University of Houston. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIA, NIAMS. **E. LaVoy:** A. Employment/Salary (full or part-time):; University of Houston. **S. Woods:** A. Employment/Salary (full or part-time):; University of Houston. **A. Hernandez:** A. Employment/Salary (full or part-time):; University of Houston. **L. Pollonini:** A. Employment/Salary (full or part-time):; University of Houston. **R. Mathew:** A. Employment/Salary (full or part-time):; University of Texas Health Science Center Houston.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.08/LL25

Topic: I.05. Working Memory

Support: NIH Training Grant 5T32 NS077889
NINDS Grant NS088555

Title: Preliminary Investigation of the Effect of Exercise on the Autoshaping Touchscreen Behavioral Task

Authors: *K. M. COTTER[1], C. M. J. STUART[1], D. MERCURIO[2], P. YANEV[2], J. TURCHAN-CHOLEWO[2], D. R. BRITSCH[1], A. J. EISCH[3], A. M. STOWE[4];
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Abstract: It is widely known that exercise is beneficial for many aspects of health, including physical, emotional, and mental, yet many of the exact mechanisms remain unknown. One of the most fundamental aspects of cognitive function is associative learning, which is often overlooked for more complex types of cognitive tasks. Autoshaping (AUTO), a Pavlovian learning task, utilizes an unconditioned reward to build associations with a conditioned stimulus (CS+) on a touchscreen platform, which has not previously been used to track cognitive decline in aged mice. We hypothesized that while both exercise and sedentary animals could learn the AUTO task, exercise in aged animals would produce quicker response times to the stimulus and to the reward. Female (11-18-month-old, n=26) CD19CL mice were split into exercise (Ex, n=15) and sedentary (Sed, n=11) groups, with exercise animals having voluntary access to monitored running wheels. After 3 weeks of exercise, all animals underwent training on the AUTO touchscreen task, made up of 2 habituation days and 3 task-training days. Mice received a one-week break, then performed a 5-day acquisition for baseline and again 2 weeks later. Mice had confirmed assignment to Ex and Sed groups after analyzing exercise activity (n=19 Sed, n=7 Ex). Primary measures were tray latency, screen latency, and the number of approaches to CS+ (rewarded) and CS- (unrewarded) stimuli. Both groups learned the association between the reward and the CS+ stimulus, as shown by the significantly lower tray latency on a CS+ trial compared to a CS- trial (3-way rmANOVA; stimulus $F(1,65)=22.19$, $p<0.0001$). Voluntary exercise had a near-significant effect on the number of CS+ trials where mice first approached the reward tray (2-way rmANOVA; $F(1,24)=3.583$, $p=0.0705$). While both Ex and Sed mice learned the task, mice that have voluntarily exercised trend toward a goal-tracking phenotype, indicated by increased CS+ trials with first approaches to the reward tray before the reward is dispensed. A second cohort is in progress, bringing the total Ex and Sed group sample sizes to 21 and 24, respectively, and future studies will look at whether exercise mitigates associative memory changes after stroke.

Disclosures: K.M. Cotter: None. **C.M.J. Stuart:** None. **D. Mercurio:** None. **P. Yanev:** None. **J. Turchan-Cholewo:** None. **D.R. Britsch:** None. **A.J. Eisch:** None. **A.M. Stowe:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.09/LL26

Topic: I.05. Working Memory

Support: R25AG086095
UF Office of the Vice President for Research

McKnight Brain Institute
UF Center for Cognitive Aging and Memory

Title: The GLP1 receptor agonist Semaglutide and caloric restriction both drive metabolic and cognitive improvements in aged rats

Authors: *J. P. GRUBBS[1], Z. A. KRUMM[1], J. L. BIZON[3], B. SETLOW[2];
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Abstract: GLP1 receptor agonists (GLP1RAs) have revolutionized metabolic medicine. Yet, despite pre-clinical and epidemiological evidence suggesting that GLP1RAs may benefit cognitive function in both aging and neurodegenerative disease, there remains limited evidence related to the effect size of this benefit or the mechanisms by which this drug class would achieve such a benefit. To evaluate the impact of a current-generation GLP1RA versus matched caloric restriction on cognitive function in aging, we assessed metabolic trajectories and performance on a prefrontal cortex-dependent delayed response working memory task in aged (~28 months, n=6-8/cohort) male and female Fischer 344 x Brown Norway F1 hybrid rats treated with either Semaglutide (20 µg/kg, 6 days/week), pair-fed to the Semaglutide group food consumption, or ad libitum-fed controls over a period of 6 weeks. We also assessed performance in ad libitum-fed young adult (~6 months) rats to establish a baseline level of accurate performance. Rats underwent behavioral testing 5 days/week. As expected, both Semaglutide and pair-feeding caused weight loss compared to ad libitum controls, with the Semaglutide group losing slightly more weight (composite placebo-subtracted weight loss versus ad lib controls: 21.33% Semaglutide, 16.12% pair-feeding, $p<0.001$ by RM ANOVA of weight trajectory for both). Body composition changes tracked weight loss trajectories, with Semaglutide rats losing slightly more fat mass than pair-fed rats. Lean mass loss was proportional to weight loss across groups, and relative grip strength did not differ between groups. In the working memory task, Semaglutide and pair-fed groups increased working memory accuracy between weeks 1 and 6 of testing (RM ANOVA, working memory delay duration X treatment group, $F_{(2,4)} >4$, $p<0.001$ for both sexes comparison), with Semaglutide rats improving more than pair-fed, especially at long retention delays. In absolute performance terms, both Semaglutide and pair-fed rats reached at least 95% of the accuracy of the young rats. The number of trials completed/session was roughly equivalent in Semaglutide and ad libitum rats, whereas pair-fed rats performed 10-20% more trials per session. Together, these data indicate that improved metabolic parameters can remediate cognitive deficits in aged rats, and that Semaglutide may provide additional benefits. Biomolecular evaluations of metabolic, inflammatory, and vascular differences between groups will be instrumental in determining mechanistic drivers of improved task performance.

Disclosures: J.P. Grubbs: None. **Z.A. Krumm:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.10/LL27

Topic: I.05. Working Memory

Title: Sex Differences among NACHO Knockout Mice and Wildtype Mice in Exercise and Novel Object Recognition

Authors: *J. SAWAH[1], K. A. MARQUEZ[2], A. GONZALEZ[3], J. SORAPURU[1], Z. HASSAN[4], Y. SHERAFAT[4];
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Abstract: Exercise has been shown to be a beneficial method in enhancing cognitive functioning. Specifically, exercise was shown to significantly increase α7 nAChR of the hippocampus. Activating the α7 nAChR is shown to improve cognition. The α7 nAChR has been shown to be dependent on the chaperone protein NACHO. Sex differences are found in both spatial memory and recognition memory in rodent models. Specifically, male mice were found to have a higher preference for exploring and remembering an object's location for long periods of time; whereas female mice developed a novelty preference and could not remember object locations. Female mice have also been shown to exhibit more forward running compared to males. For this study, we wanted to assess the sex differences in running behavior and object recognition among wildtype and NACHO KO mice. For this study, half of the groups engaged in three weeks of wheel running and the other half did not. After these three weeks, mice were assessed for recognition of memory using the Novel Object Recognition test. The results in this study revealed no sex differences among wildtype and NACHO KO mice for exercise and object recognition. The results also revealed no sex differences among wildtype and NACHO KO mice in the non-exercise group. Gaining a better understanding of how NACHO expression impacts running behavior and novel object recognition between males and females can lead to the development of treatment aimed at manipulating NACHO differently between sexes. Future studies should examine how exercise impacts the expression of NACHO.

Disclosures: J. Sawah: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **K.A. Marquez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **A. Gonzalez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **J. Sorapuru:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **Z. Hassan:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **Y. Sherafat:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.11/Web Only

Topic: I.05. Working Memory

Support: UNAM DGAPA PAPIIT IG300124

Title: Minor depressive symptoms are associated with memory decline across the adult lifespan

Authors: *S. CANSINO[1], F. TORRES-TREJO[1], C. ESTRADA MANILLA[1], S. RUIZ VELASCO ACOSTA[2];
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Abstract: Individuals with a diagnosis of major depressive disorder exhibit cognitive difficulties. However, the effects of subclinical or subthreshold depressive symptoms on cognition are less known. The aim of the present cross-sectional study was to determine the possible influence of minor depressive symptoms on working memory and episodic memory. Depressive symptoms were assessed with the Beck Depression Inventory. Working memory was examined in a sample of 1662 participants, and episodic memory was examined in a subsample of 1557 individuals. All the subjects were healthy adults between the ages of 21 and 80 years. All the memory tasks were computerized. Working memory was assessed in the spatial and verbal domains at two levels of difficulty. With respect to episodic memory, we evaluated recognition and recollection. Hierarchical regression models demonstrated that depressive symptoms predicted lower memory performance in all tasks and processes after controlling for age, sex, years of education, vocabulary scores, and Mini-Mental State Examination scores. Minor depressive symptoms are powerful enough to be negatively associated with working and episodic memory performance, and stronger associations were observed as depressive symptoms worsen, indicating that their association is proportional to their number and intensity. Both types of memory are essential for performing everyday activities and preserving autonomy.

Disclosures: S. Cansino: None. **F. Torres-Trejo:** None. **C. Estrada Manilla:** None. **S. ruiz velasco acosta:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.12/LL28

Topic: I.05. Working Memory

Support: NIH R21MH130902

Title: Role of oligodendrocyte RFWD2 in cognitive function

Authors: E. Q. YU[1,2], R. FEHER[3], *X. MA[3];
[1]Univ. of Connecticut Hlth., High Sch. Mentoring Program, Farmington, CT; [2]William H. Hall High Sch., West Hartford, CT; [3]Neurosci., Univ. of Connecticut Hlth., Farmington, CT

Abstract: Oligodendrocytes, the cells responsible for generating and maintaining the myelin sheath surrounding neuronal axons, are essential for normal brain function. Dysfunction of these cells has been implicated in psychiatric and neurodevelopmental disorders associated with working memory deficits. However, the mechanisms by which oligodendrocyte dysfunction contributes to these cognitive deficits remain poorly understood. RFWD2, also known as COP1, is an E3 ubiquitin ligase that regulates protein stability by targeting specific substrates for ubiquitination and degradation. Dysregulation of E3 ubiquitin ligases has increasingly been linked to neurodevelopmental and psychiatric disorders. Notably, some individuals with autism carry three copies of the Rfwd2 gene. Consistently, our previous studies showed that Rfwd2 conditional overexpression mice, which express three copies of Rfwd2 throughout the brain, exhibit autism-like behaviors accompanied by reduced dendritic spine density and impaired synaptic function in medial prefrontal cortex (mPFC) pyramidal neurons. However, the role of RFWD2 in oligodendrocytes remains unknown. To model the increased Rfwd2 gene dosage observed in some individuals with autism, we generated *Rfwd2* conditional overexpression (***Rfwd2*^{cOE}**) mice that specifically overexpress RFWD2 in oligodendrocytes. These mice were produced by crossing Rfwd2-loxP mice with Oligo2-Cre mice. We found that RFWD2 is expressed in oligodendrocytes within the mouse prefrontal cortex and that RFWD2 protein levels are elevated in the mPFC oligodendrocytes of *Rfwd2*^{cOE} mice. Behaviorally, *Rfwd2*^{cOE} mice exhibited deficits in both spatial working memory, as assessed by the Y-maze test, and recognition memory, as measured by the novel object recognition test, compared with littermate controls. In addition, these mice displayed increased anxiety-like behavior in both the open field and elevated zero maze tests. Together, these findings identify a previously unrecognized role for oligodendrocyte RFWD2 in cognitive and emotional behaviors. Given the well-established relationship/correlation between dendritic spine structure, synaptic function, and cognition, these results suggest that oligodendrocyte RFWD2 influences dendritic spines and synaptic function in the brain regions associated with cognition (Yu and Feher contributed equally)

Disclosures: E.Q. Yu: None. **R. Feher:** None. **X. Ma:** None.

Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.13/LL29

Topic: I.05. Working Memory

Title: Impact of acute microplastic exposure on working memory in a rodent model of Alzheimer's disease

Authors: *E. K. FREDERICK[1], C. T. DIXON[2], D. K. SMITH-CORBIN[2], M. L. ECKARD[2], S. O'BRIEN[2], D. M. HAYES[3];
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Abstract: Plastic pollution is an ongoing, detrimental environmental concern. Specifically, plastic does not fully degrade but rather breaks down to the micro-particle scale and stays in our ecosystems. These microplastics, then, can passively invade our environments and bodies where they act as pervasive pollutants. The exact impact of this microplastic exposure is unknown, but evidence suggests that environmental risk factors like plastic pollution could contribute to widespread neurodegenerative disorders such as Alzheimer's disease (AD). AD, the most common form of dementia, is a terminal degenerative brain disorder that results in the capacity to live a typical lifestyle being severely impaired. A hallmark characteristic of AD is the loss of cholinergic signaling within the brain, leading to impairments in working memory processes. Administration of Scopolamine, a non-selective muscarinic antagonist for acetylcholine, has been widely used as an animal model of AD due to the similar pathological changes mirrored in humans. However, the combined damage from microplastic exposure and AD has yet to be studied systematically. In rodents, typical passive human exposure to microplastics can be modeled with a single acute exposure to polyethylene microplastics via oral gavage without causing unnecessary harm to the animals. Thus, the current study aimed to examine cognitive alterations following a single polyethylene-microplastic exposure in a repeated administration scopolamine-induced model of AD using a delayed-match-to-position (DMTP) task to assess working memory in rats. The number of correct responses, time latency, and trial omissions as measures of accuracy, retention, and forgetting for the DMTP task were recorded and analyzed separately. All dependent measures displayed similar overall patterns across stages in mixed model ANOVAs. Specifically, scopolamine administration impaired task performance in week 1, scores improved slightly in week 2 of administration, and animal behaviors returned to pre-administration levels by the end of the washout phase (week 3). However, microplastic exposure did not impact any facet of working memory in this model throughout the DMTP task. This study provides an initial exploration into understanding the overall impacts that microplastics may have on physiology and behavior. Future studies should consider administering microplastics earlier in the experimental timeline or using a chronic model of exposure.

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Poster

PSTR333: Behavioral Studies of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR333.14/LL30

Topic: I.05. Working Memory

Support: NIH RO1AG073152

Title: Reactive balance performance during dual-task walking in older adults with mild cognitive impairment across multiple cognitive domains

Authors: *S. DESHMUKH[1], J. PITTS[2], T. S. BHATT[2];
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Abstract: Older adults with mild cognitive impairment (OAwMCI) exhibit deficits in both cognitive and motor function, leading to greater cognitive-motor interference (CMI) than cognitively intact older adults (CIOA) during dual-tasking. OAwMCI show higher CMI than CIOA during both volitional balance tasks (e.g., walking) and reactive balance tasks (e.g., recovering from unexpected slip-like perturbations), and one study from our lab found that visuomotor tasks were particularly challenging for both OAwMCI and CIOA during reactive balance control. However, this study only induced perturbations during standing, while most falls in daily living occur from perturbations during walking (e.g., slips, trips), which might result in different CMI patterns due to differences in the biomechanical, sensorimotor, and neural control of walking vs. standing. Therefore, this study examined the effects of four cognitive tasks representing different cognitive domains on reactive balance performance in OAwMCI and CIOA during slip-like walking perturbations. 30 OAwMCI and 31 CIOA completed two visuomotor tasks (Target, Tracking) and two executive function/working memory tasks [Auditory Clock Test (ACT) and Letter Number Sequencing (LNS)], while walking and experiencing unexpected slip-like perturbations (dual-task). To assess single task motor and cognitive performance, perturbations were also delivered without cognitive tasks, and cognitive tasks were completed while standing. Reactive balance performance was quantified using margin of stability (MOS) at recovery touchdown, and cognitive performance was determined by the performance error (visuomotor tasks), accuracy (ACT), or number of correct responses (LNS). Both groups demonstrated reduced MOS during dual task conditions compared to single task, with greater reductions in OAwMCI. Both groups also demonstrated impaired cognitive performance on visuomotor tasks and the LNS during dual task conditions, with greater reductions in LNS performance in OAwMCI. Cognitive costs (% change in cognitive performance in single vs. dual task) were higher in OAwMCI compared to CIOA, and were higher during visuomotor tasks compared to the ACT or LNS for both groups. Overall, these findings indicate that dual tasking may increase slip-related fall risk while walking in older adults, with OAwMCI exhibiting greater vulnerability to CMI than CIOA. Further, daily living tasks involving visuomotor processing may place especially high demands on shared cognitive-motor resources during reactive balance control, and potentially increase fall risk more than executive function/working memory tasks.

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Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.01/LL31

Topic: I.07. Long-Term Memory

Support: Council for the Arts at MIT
Mass Cultural Council
Somerville Arts Council
Malden Cultural Council

Title: Event-State Geometry and Predictive Structure in Autobiographical Narrative

Authors: *J. SARINANA, Jr.;
MIT, Cambridge, MA

Abstract: Autobiographical narratives contain structured sequences of events, but the representational units underlying those sequences are not predefined. This work presents a proof-of-principle computational framework for reconstructing event-state spaces from autobiographical narrative and analyzing their representational geometry, transition dynamics, and multi-step predictive structure within a unified analytical pipeline. Narrative excerpts from semi-structured autobiographical interviews (N = 5 participants) were analyzed using a schema-constrained large language model (LLM) workflow composed of separate thematic and event-structure analysis streams. Event-structure annotations were constrained by theory-guided categorical ontologies derived from frameworks of episodic and hippocampal function, while thematic structure was generated through a separate semantic integration pipeline. Event boundaries were defined using explicit state-transition criteria over contextual, anchoring, and representational features. Excerpts were aggregated into event-states and embedded into a 5-dimensional representational space using multiple correspondence analysis (MCA). Density-derived basin-states were then used to estimate transition dynamics and successor representations over multi-step event trajectories. The reconstructed state space showed interpretable large-scale organization associated with contextual and thematic structure. Basin-level routing patterns were context-dependent and showed limited correspondence with local feature similarity, indicating that representational similarity alone did not determine transition structure. Successor-derived predictive structure showed moderate but non-isomorphic correspondence with representational geometry, suggesting that multi-step predictive organization is constrained by, but not reducible to, local representational similarity or one-step transitions. The findings provide evidence that naturalistic autobiographical narratives can be transformed into structured, analyzable event-state systems using schema-constrained LLM workflows with explicit provenance and event-boundary rules. The framework provides a computational approach for studying episodic event organization in naturalistic cognition and establishes a basis for future comparisons between narrative-derived state structure and neural network activity associated with cognitive exploration.

Disclosures: J. Sarinana: None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.02/LL32

Topic: I.07. Long-Term Memory

Support: NIH Grant R01NS109367
NIH Grant R01NS115929
NIH Grant R01DC018805
NSF Grant IIS-2309057

Title: Spectrotemporal neural signatures predict cognitive boundaries during naturalistic events

Authors: *F. ZHOU[1], A. KHALILIAN-GOURTANI[2], A. MICHALAK[2], P. A. ROZMAN[3], W. K. DOYLE[3], D. FRIEDMAN[2], A. FLINKER[2,1];
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Abstract: The brain automatically parses continuous experience into discrete events by identifying cognitive boundaries that mark meaningful transitions. However, the electrophysiological signatures underlying this boundary detection during real-world experiences remain poorly understood. To address this question, we recorded intracranial neural activity from the human medial temporal lobe (MTL) during naturalistic movie viewing. The stimulus contained four distinct yet interwoven storylines, providing a unique framework for examining multiple forms of event boundaries. Based on the narrative structure, we defined four categories: hard boundaries (transitions between different storylines), soft switch boundaries (transitions between different characters or objects within the same storyline), soft same boundaries (transitions between segments of the same object within the same storyline such as an abrupt zoom-in), and no boundaries (continuous narrative transitions without segmentation). We found that amygdala electrodes exhibited an early gamma-band response (~200 ms) following both hard boundaries and soft switch boundaries, whereas hippocampus electrodes showed a later theta-band response (~500 ms) selectively associated with hard boundaries. To further characterize these functional distinctions, we trained event-boundary decoding models using convolutional MiniRocket features on the movie-viewing data with a sliding-window approach. The models achieved peak accuracies of 82% and 77% for amygdala and hippocampus, respectively (chance levels = 50%), indicating their robust neural involvement in boundary identification. Critically, we then applied the decoders to multi-day naturalistic recordings collected from the same participants to test for real-world generalizability. Decoding of daily-life event boundaries demonstrated that amygdala activity tracked transient transitions in attended naturalistic objects (e.g., shifting gaze from a lunch meal to dessert), whereas hippocampal activity preferentially marked the onset and offset of meaningful events (e.g., finishing a meal or beginning to drink coffee). Together, these findings provide spectrotemporal-specific evidence for dissociable roles of subregions within the human MTL during naturalistic events and offer novel insights into the mechanisms underlying boundary detection.

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Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.03/LL33

Topic: I.07. Long-Term Memory

Support: This work was supported by the Intramural Research Program of NINDS

Title: Stable intracranial electrode communities support encoding-retrieval reinstatement of co-rippling during human associative memory

Authors: *M. J. R. LIM[1], M. LICHTENFELD[4], O. E. FRUCHET[2], S. INATI[3], K. A. ZAGHLOUL[1];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, [2]Neurosurg., [3]NIH, Bethesda, MD; [4]NIH, Natl. Inst. of Neurolog. Disorders & Stroke, Washington, DC

Abstract: Introduction: While pairwise co-rippling between hippocampus and neocortex has been linked to successful retrieval, whether stable multi-electrode communities of co-rippling electrodes support distinct aspects of associative memory in humans remains unknown.
Methods: Intracranial EEG was recorded from 25 patients with medically refractory epilepsy (57 sessions) performing a verbal paired-associate learning task. Significant co-rippling electrode pairs were identified by cross-correlation (±250ms lag) with 10000 circular-shift null permutations (FDR $Q<0.01$). A multi-layer generalised Louvain algorithm ($\gamma=1$, $\omega=1$) detected communities stable across sessions. For each community, we tested: (i) significantly higher ripple rate during correct vs. wrong retrieval (cluster-corrected sign-flip permutation test, $p<0.05$); (ii) decoding of correct or wrong retrieval using L2-regularised logistic regression trained on ripple durations during encoding trials (cluster-corrected label-shuffle permutation test, $p<0.05$); and (iii) encoding-retrieval reinstatement using Jaccard similarity of rippling channels (sign-flip permutation test, $p<0.05$).
Results: Across 25 patients, we identified 142 cross-session communities. Twenty-two communities in 16 patients showed significantly elevated ripple rates prior to correct vs. wrong retrieval. A largely distinct set of 22 communities in 17 patients decoded memory outcome above chance (AUC: 0.56-0.74, mean 0.64; permutation test, $p<0.05$), with only 7 communities meeting significance in both criteria. In ripple-rate communities, the same channels were more likely to be active during both encoding and correct retrieval compared to wrong retrieval (correct 0.30 ± 0.02, wrong 0.28 ± 0.02; sign-flip permutation test, $n=15$ patients, $p=0.038$); this effect was absent in non-significant communities, confirming specificity. Reinstated channels showed temporal structure during encoding at 2500-3000ms after cue presentation and up to 600-200ms prior to retrieval.
Conclusion: Cross-session co-rippling communities distributed throughout the human cortex reveal a dissociation between rate-based and information-based memory signals. Communities exhibit reinstated ripple co-activation patterns across encoding and retrieval, suggesting coordinated ripple replay as a substrate for successful associative memory.

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Poster

PSTR334: Episodic and Episodic-Like Memory

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Program #/Poster #: PSTR334.04/LL34

Topic: I.07. Long-Term Memory

Support: R01 MH119099

Title: Cortical and Hippocampal Pathways to Mental Continuity

Authors: *X. LI[1], H. LEE[3], C. J. HONEY[2];
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD; [3]Dept. of Psychological Sci., Purdue Univ., West Lafayette, IN

Abstract: Naturalistic experiences such as reading and conversing are regularly interrupted; and yet in many cases we are able to spontaneously retain the mental context associated with our primary task. Existing memory models cannot easily account for this. Classic working memory maintains the same neural pattern for ~10 s with limited capacity and requires active control to hold it in place, while long-term memory requires hippocampal encoding and retrieval. We propose an intermediate-level process (a background process) that bridges working and long-term memory by carrying a slowly evolving, top-level narrative scaffold across interruption without requiring active maintenance. We collected fMRI data while participants (N=73) listened to coherent (or incoherent) 14-min narratives that were interrupted for ~25 seconds after every ~40 seconds with silent pauses or a theory-of-mind (ToM) competing task. In interrupted participants, hippocampal (HC) activity transiently increased at interruption onset. Individuals with larger BOLD activations at interruption onset recalled the story better ($r=.465$, $p<.001$), consistent with the notion that HC activity reflects encoding of the preceding narrative epoch (Ben-Yakov & Dudai, 2011). Moreover, the posterior-medial cortex (PMC) maintained narrative information throughout the interruption period in the form of a reliable, epoch-selective, and gradually evolving multivoxel pattern. This interruption pattern persisted in PMC both during silent pauses and even during the ToM interruptions (all $ps<.05$). This persisting pattern was inverted from its preceding story-phase pattern ($r=-.240$, $p<.001$), with different epochs showing distinct inverted patterns ($p=.001$). Moreover, individuals with more canonical PMC patterns during the interruption phases also exhibited a "restoration of narrative context effect": their post-interruption neural activations more closely matched the activity pattern in participants who were never interrupted ($\beta=.386$, $p<.001$). This was true, even when controlling for HC boundary activity ($\beta=.093$, $p=.005$). The PMC pattern reliability also predicted better narrative memory ($\beta=.764$, $p=.004$), and it did so more strongly than HC activity ($\beta=.232$, $p=.017$). These findings implicate two complementary pathways supporting mental continuity: a hippocampal indexing route and a PMC background process that holds the narrative scaffold in a transformed code.

Disclosures: X. Li: None. **H. Lee:** None. **C.J. Honey:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.05/LL35

Topic: I.07. Long-Term Memory

Support: ONR Grant N00014-17-1-2961

Title: A neural network model of how event schemas shape episodic memory

Authors: *C. SUN, Y. ZHENG, R. O'REILLY, C. RANGANATH;
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Abstract: Prior knowledge about how familiar events typically unfold—an event schema—powerfully shapes what we remember. Schemas aid memory for schema-consistent information and, paradoxically, also aid memory for schema-violating information, producing a U-shaped relationship between memory and expectedness. However, there is still little mechanistic understanding of how event schemas and episodic memory interact to give rise these effects. We present a neural network model in which a schema system and an episodic memory system cooperate to explain these effects. In the model, each experience combines features that follow a predictable, schema-governed structure with specific features unique to that experience. Because the schema can anticipate the predictable features but not the specific ones, the two are handled differently: the schema supplies the predictable features during both perception and recall, while episodic memory specializes in storing the idiosyncratic details. This division of labor lets a schema-equipped model adapt to new events faster and recall experiences more accurately than a model without a schema, and it reproduces the U-shaped memory effect—schema-consistent experiences are well remembered because the schema reconstructs them, while schema-violating experiences are well remembered because their surprise drives strong episodic encoding; experiences of intermediate expectedness fare worst. The model thus shows how schemas and episodic memory can work together, rather than in opposition, to shape what we remember, and yields testable predictions that schematic and specific features of an experience should show dissociable memory signatures.

Disclosures: C. Sun: None. **Y. Zheng:** None. **R. O'Reilly:** None. **C. Ranganath:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.06/LL36

Topic: I.07. Long-Term Memory

Title: Decoding the deliberative and strategic effects of forward and backward temporal structure in episodic memory retrieval

Authors: R. M. GUTIERREZ, *J. D. JOHNSON;
Psychological Sci., Univ. of Missouri, Columbia, MO

Abstract: It is well established that episodic memories are supported by associations formed both across stimuli within an event and with their unique spatial and temporal contexts. Numerous studies employing behavioral and neural measures, often in combination with computational modeling, have investigated the roles of associative and contextual information in effective encoding and in guiding search processing and strategies that can lead to successful retrieval. Additionally, although there is extensive behavioral evidence that retrieving sequences of stimuli/events in the forward direction (i.e., in the order originally experienced) is more frequent and accurate than doing so in the backward direction, little research has been directed at understanding the neural processes that might underlie this asymmetry in the temporal direction of retrieval. Here, we report on a procedure that uses directional (forward vs. backward) cued recall in combination with scalp EEG to uncover differences in neural activity with respect to retrieval direction. Our procedure also tested the extent to which knowledge about direction can be supported by strategic processing by cuing the upcoming direction either before (pre-cue) or after (post-cue) encoding. Subjects (N=48) encoded short lists of words and were then provided one word along with arrows indicating whether to recall the immediately preceding (backward) or following (forward) list words. Importantly, the directional asymmetry in behavioral performance was eliminated, allowing neural differences to be interpreted beyond less-interesting factors such as retrieval difficulty and success. Multivariate decoding of oscillatory activity in the EEG revealed lateralized, high-frequency (gamma band) differences according to retrieval direction during the search and deliberation period preceding report of recalled words. The pre- vs. post-cue manipulation, however, had no effect on behavioral or neural differences, suggesting that prior knowledge does not lead to additional encoding or retrieval strategies being employed in service of direction. Overall, the present findings of temporal direction engaging distinct neural processes are consistent with gamma activity shown in previous studies using intracranial and scalp EEG that have related context to the accuracy of episodic retrieval.

Disclosures: R.M. Gutierrez: None. **J.D. Johnson:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.07/LL37

Topic: I.07. Long-Term Memory

Title: Longitudinal Stability of Positive Autobiographical Memories Across Adolescence

Authors: *X. A. HUANG, T. SAVALIA, A. O. COHEN;
Psychology, Emory Univ., Atlanta, GA

Abstract: Adolescence and young adulthood are critical periods of identity formation during which autobiographical memories play an important role in shaping a sense of self. Individuals tend to show a bias towards recalling positive life events that often retain their salience over time, contributing to well-being and self-identity. At the neural level, previous studies have shown that neural representations of autobiographical memories evolve over periods ranging from months to several years, especially within the hippocampus and ventromedial prefrontal cortex (vmPFC). However, less is known about whether the positive affect associated with specific autobiographical memories shows similar stability over multi-year intervals, and how changes in affect might relate to longitudinal changes in their neural mechanisms.To address these research gaps, we collected data from 132 participants ages 10-25 over the past two years and have thus far followed up with 29 participants. Participants generated specific positive autobiographical memories associated with cue words and retrieved these memories during an fMRI scan at baseline. Immediately following retrieval of each memory, participants rated the positive affect linked to each event. Approximately two years later, participants completed the same autobiographical memory retrieval task in the fMRI scanner. Preliminary behavioral analyses from 29 participants indicate that the ratings across the two-year interval were stable. Ratings were significantly correlated across time points (partial $r = .32$, $p < .001$, controlling for age), and mean change in ratings was minimal. Age was not significantly associated with rating stability. Preliminary neuroimaging analyses of the baseline scans identified engagement of the default mode network (DMN) during retrieval of positive autobiographical memories. Ongoing neuroimaging analyses will examine whether neural mechanisms within hippocampal, vmPFC, and DMN show similar longitudinal stability across adolescence and young adulthood. These preliminary findings suggest that the affective value associated with positive autobiographical memories remains relatively stable over time.

Disclosures: X.A. Huang: None. **T. Savalia:** None. **A.O. Cohen:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.08/LL38

Topic: I.07. Long-Term Memory

Support: NRF Grant RS-2023-00265406
NRF Grant 2023R1A2C2005587
Global-LAMP Program of NRF Grant RS-2023-00301976
Creative-Pioneering Researchers Program at Seoul National University

Title: Anatomy-Guided MEG Source Localization Enhances Hippocampal Spectral Precision During Episodic Memory: Validation against intracranial EEG

Authors: ***S. YU**[1], S. KIM[2], S. LEE[1];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Pediatric Neurol., Severance Hosp., Seoul, Korea, Republic of

Abstract: Human hippocampal (HP) oscillations have been primarily studied using intracranial EEG (iEEG) in epilepsy patients, highlighting the need for non-invasive approaches in human neuroscience. Magnetoencephalography (MEG) can reconstruct source signals with high spatio-temporal resolution, but the reliability of source localization for deep brain regions remains controversial. Recent attempts to improve these algorithms face two main limitations: first, they are predominantly data-driven and fail to incorporate anatomical constraints such as HP laminar structure; second, they often rely on resting-state data rather than cognitive tasks that directly engage the HP. In this study, we aimed to reconstruct HP source activity using anatomical constraints to enhance the precision of oscillatory profiles during cognitive tasks. We recorded MEG and iEEG across two sessions in five epilepsy patients while they performed a what-where-when episodic memory task. To reconstruct source activity from MEG data that corresponded to the iEEG electrode locations, we developed a novel anatomy-guided approach in which source orientation was estimated along the alignment of pyramidal cells within the HP layers using HippUnfold. To compensate for the difference in the 1/f aperiodic slopes between modalities (approximately 1.2 and 1.5 for MEG and iEEG, respectively), the aperiodic component was subtracted from the raw spectral power.The orientation normal to the HP laminar structure differed significantly from that derived using conventional data-driven methods and showed improved similarity with the iEEG spectra in the HP during episodic memory encoding. This improvement was most pronounced in the delta (2-5Hz) and gamma (30-50Hz) bands. Furthermore, this orientation difference was linked to the dissimilarity of the lead field matrix, which encodes the sensor topography—reflecting the extent to which specific sensors capture activity from a given voxel.Our approach may enhance the estimation of HP spectral profiles and facilitate the investigation of sophisticated electrophysiological studies of human HP memory function. Further validation is needed to confirm its reliability and task-dependent functional specificity.

Disclosures: S. Yu: None. **S. Kim:** None. **S. Lee:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.09/LL39

Topic: I.07. Long-Term Memory

Support: NRF Global-LAMP Program, RS-2023-00301976
NRF Grant RS-2023-00265406
NRF Grant 2023R1A2C2005587
Creative-Pioneering Researchers Program at Seoul National University

Title: Separable structural, affective, and metacognitive dimensions of subjective cognitive decline in Korean older adults

Authors: *L. SHIM[1], M. HWANG[2], S. LEE[2];
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Abstract: Cognitive aging is characterized by episodic memory decline, and individual reports of memory impairment are commonly measured by subjective cognitive decline (SCD) surveys. Previous studies have linked SCD to medial temporal lobe (MTL) and default-mode regions vulnerable to neurodegeneration, yet SCD may also reflect affective and metacognitive processes. We examined whether SCD in a Korean aging cohort reflects objective memory decline, affective mood, or task-based self-evaluation. Participants were 169 healthy Korean adults aged 50-86 years (110 females); 133 had usable task-fMRI data and 90 had self-estimation data. Measures included What-Where-When (WWW) scene memory performance, RBANS delayed memory and total scores, SCD, depressive symptoms, hippocampal/MTL volumes, cortical thickness, voxel-based morphometry, and task-fMRI. We first confirmed a behavioral-structural dissociation: hippocampal volume predicted RBANS delayed memory but not SCD, whereas SCD was more strongly associated with depressive symptoms. To test whether subjective complaints corresponded to objective performance, SCD discrepancy was defined as SCD relative to an RBANS-WWW objective composite. This questionnaire-level discrepancy showed weak and inconsistent neural correlates, suggesting that SCD alone did not map directly onto a single neural aging marker. Task-based metacognition was then defined within the WWW task as self-estimated performance relative to actual performance. Directional metacognitive error indexed over- versus under-estimation, whereas absolute error indexed the magnitude of self-performance mismatch. Older age was associated with greater absolute metacognitive error, indicating reduced self-evaluation accuracy with aging. In contrast, directional overestimation bias was associated with lower frontal/temporal cortical thickness, even after controlling for age and absolute error. When participants were split into under- and over-estimators, overestimators showed lower MTL cortical thickness and steeper age-related cortical thinning. Depressive symptoms did not predict directional or absolute metacognitive error, supporting a dissociation between affective mood and task-based metacognition. Together, these findings suggest partly separable dimensions of cognitive aging: a structural-memory dimension linking hippocampal integrity to objective memory, a subjective-affective dimension linking SCD to depressive symptoms, and a metacognitive dimension linking task-based self-evaluation bias to fronto-temporal cortical thinning.

Disclosures: L. Shim: None. **M. Hwang:** None. **S. Lee:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

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NRF Grant 2023R1A2C2005587
Global-LAMP Program of NRF Grant RS-2023-00301976
Creative-Pioneering Researchers Program at Seoul National University

Title: Canonical neural dynamics capture temporal event structure in the human parietal cortex and hippocampal formation

Authors: *H. KANG, J. SHIN, S. LEE;
Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: When individuals experience identical episodes (e.g., movie), their brains exhibit shared activity dynamics. Because most of these studies involved perceptually and semantically complex stimuli, it is unknown whether the shared neural dynamics represent unique episodes or a more abstract event structure. Here we investigated intersubject correlations in brain responses to unique combinations of objects and locations presented in a fixed, time-locked sequence. 33 participants (mean age = 24.12, 12 females) were tested using 3T fMRI, and 20 participants (mean age=24.5, 10 females) were tested using 7T fMRI to investigate hippocampal (HP) subfield activity. In each trial, participants watched five objects sequentially placed into baskets scattered within a virtual room, followed by a delayed retrieval task. Each participant performed 8 trials. Individual-to-canonical similarity (ICS) was defined as the correlation between an individual's and the group average dynamics, reflecting how well each participant follows the canonical pattern. Using 3T fMRI, we found that while significant ICS spanned most cortical regions, the dorsolateral prefrontal, inferior parietal, and lateral temporal cortices showed positive correlations with memory accuracy and mediated the effect of parahippocampal cortex (PHC) on memory performance. Further analysis revealed that the superior parietal, premotor, dorsal/ventral visual cortices reliably tracked event timing, fluctuating along the sequential event progression. To probe the functional role of MTL dynamics, we employed inter-subject representational similarity using to correlate subject-pair neural similarity matrices, based on trial-by-trial activity dynamics of HP subfields and the PHC, with behavioral response similarity matrices containing retrieved temporal sequences. In the 3T data, we found that neural dynamics in the left HP and left PHC cortex closely tracked the behavioral response. 7T data revealed that the effect is strongest in the left anterior subiculum and anterior CA1. Together, these findings suggest that content-general temporal event memory structure is reflected across the cortex in a canonical way across individuals, while specific memory sequences are represented in a canonical way in the MTL.

Disclosures: H. Kang: None. **J. Shin:** None. **S. Lee:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.11/Web Only

Topic: I.07. Long-Term Memory

Title: Interactive Effects of Openness and Extraversion on Episodic Memory: A Sex- and Domain-Specific Personality-Clustering Approach

Authors: *S. HEIDARI[1,2], N. ABBASIAN[2], A. GHADERI[3,2];
[1]Univ. of Esfahan, Esfahan, Iran, Islamic Republic of; [2]Iranian Neurowave Lab., Isfahan, Iran, Islamic Republic of; [3]Özyegin Univ., Istanbul, Turkey

Abstract: Individual variability in episodic memory is substantial, yet how interactive personality configurations shape recall remains poorly understood. This study used a person-centered, multivariate clustering approach to investigate whether distinct profiles of openness (O) and extraversion (E) differentially map onto domain-specific memory, and whether these associations are modulated by sex.We analyzed data from healthy young adults in the Human Connectome Project (HCP; N = 1206, ages 22-36; 656 females). O and E scores from the NEO-FFI were subjected to k-means clustering, with the Calinski-Harabasz criterion used to determine optimal solutions. The clustering procedure was applied once to the full sample and once separately for males and females. Verbal and visual episodic memory were assessed via the Penn Word Memory Test (PWMT) and the NIH Toolbox Picture Sequence Memory Test (PSMT). Permutation-based t-tests (50,000 iterations, FDR-corrected $q < 0.05$) evaluated cluster differences within each group (full sample, females, males) and separately for the PWMT and PSMT.The Calinski-Harabasz criterion supported a 3-cluster solution for the full sample. For the full sample, the low-E/high-O cluster showed significantly lower scores than the other clusters in PWMT, and the high-O/high-E cluster outperformed both other clusters in PSMT. Sex-stratified analyses revealed distinct clustering patterns: females exhibited a stable 3-cluster structure, whereas males showed a more differentiated organization, with a local maximum at a 12-cluster solution. In females, cluster differences were primarily observed in verbal memory, where the high-O/high-E cluster showed significantly better PWMT scores than the other profiles. In males, cluster-specific effects emerged in visual memory, with the high-O/high-E profile showing significantly better PSMT scores than the low-O/high-E profile. These findings suggest that interactive O-E configurations capture meaningful variance in episodic memory more effectively than isolated traits. The sex- and domain-specific patterns further indicate that verbal and visual episodic memory may rely on partially distinct neural systems, with personality configurations shaping their engagement.

Disclosures: S. Heidari: None. **N. Abbasian:** None. **A. Ghaderi:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.12/LL41

Topic: I.07. Long-Term Memory

Support: R01 MH119099
NSF CAREER
Discovery Grant RGPIN-2022-04494

Title: Neural basis of persistent mental content

Authors: *G. KRESSIN PALACIOS[1], X. LI[1], B. BELLANA[2], C. J. HONEY[1];
[1]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Psychology, Glendon Campus, York Univ., Toronto, ON, Canada

Abstract: Some thoughts and experiences persist in our minds on the scale of minutes. This persistence can be beneficial, enabling us to find creative solutions to problems, but it can also be detrimental, as in the case of repetitive or unwanted thoughts. What mechanisms underlie the persistence of mental content? We quantified the persistence of mental content by asking participants to generate word chains before and after reading an immersive story. After reading, participants generated more story-related words than before and reported lingering thoughts about the story. This effect was not eliminated by explicit instructions to suppress story-related thoughts, nor by distractor tasks that interfere with short-term memory. We hypothesized that persistent content could be supported by (i) punctate instances of long-term memory retrieval and (ii) a persistent high-level event representation. To test for each of these possibilities, we collected fMRI data from 76 participants who performed free association before and after reading. First, generating story-related words was associated with increased activity in precuneus, posterior cingulate cortex - regions that are linked to long-term memory retrieval. However, follow-up analyses found no BOLD changes in the hippocampus when the story-related words were generated. Second, we found preliminary evidence for an angular gyrus multivoxel pattern that persisted in an inverted format following the end of the story. These results point towards an account of persistent mental content in which both the spontaneous retrieval of story content and the persistence of an inverted event representation underlie the mental persistence of recent experiences.

Disclosures: G. Kressin Palacios: None. **X. Li:** None. **B. Bellana:** None. **C.J. Honey:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.13/LL42

Topic: I.07. Long-Term Memory

Support: NeurTex Brain Research Institute

Title: Encoding activity predicts distinct single-neuron recognition signals for working and long-term memory in the human hippocampus

Authors: *C. W. TALLMAN[1], J. T. WIXTED[1], P. N. STEINMETZ[2];
[1]Psychology, UC San Diego, La Jolla, CA; [2]NeurTex Brain Res. Inst., Dallas, TX

Abstract: Complementary learning systems theory holds that neocortex stores distributed overlapping codes whereas hippocampus supports sparse, pattern-separated episodic coding, though recent models suggest that distinct hippocampal pathways can support both schemes (Schapiro et al., 2017). Consistent with this view, single-neuron studies in epilepsy patients have identified two recognition signals: a generic signal characterized by increased mean firing across medial temporal lobe and neocortical regions, and a hippocampal item-specific signal characterized by increased spike-count skewness among few strongly firing neurons. The item-specific signal appears selectively for remembered items with relatively increased encoding activity but has been examined only during delayed study-test recognition (Tallman et al., 2025). We asked whether encoding activity and retrieval demand both determine whether the hippocampus expresses the item-specific or generic memory signal during working memory (WM) and long-term memory (LTM). Activity was recorded from 396 hippocampal neurons, along with amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC) neurons, while 34 epilepsy patients completed continuous word recognition at lags of 0-31 intervening items. Retrieval demand was grouped by lag as WM (0-3) or LTM (7-31). Encoding firing patterns were classified as Low-High, reflecting low pre-stimulus and high during-stimulus firing, or High-High, reflecting consistently elevated firing. Repeated and novel spike-count distributions were compared using mean and skewness statistics with permutation tests and FDR correction. Low-High items showed increased skewness only in hippocampus during LTM (Δ = 2.10, $p = 0.006$), and this increase was greater for LTM than WM ($\Delta = 2.01$, $p = 0.027$). High-High items showed no skewness differences in the hippocampus or any other region. Instead, High-High items showed increased mean firing in hippocampus during both LTM ($\Delta = 0.08$, $p < 0.001$) and WM ($\Delta = 0.10$, $p < 0.001$), with the WM generic signal extending to amygdala (Δ = 0.03, $p = 0.014$), ACC ($\Delta = 0.09$, $p < 0.001$), and PFC ($\Delta = 0.06$, $p < 0.001$). These findings suggest that encoding activity predicts distinct recognition signals. Sparse item-specific recognition was selective to Low-High items during LTM and confined to hippocampus, whereas generic recognition was preferentially expressed for High-High items across WM and LTM and extended to medial temporal and neocortical regions. Thus, encoding activity and retrieval demand both determine which recognition signal dominates.

Disclosures: C.W. Tallman: None. **J.T. Wixted:** None. **P.N. Steinmetz:** None.

Poster

PSTR334: Episodic and Episodic-Like Memory

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR334.14/LL43

Topic: I.07. Long-Term Memory

Title: Depression Selectively Impairs Temporal Context Organization in Episodic Memory

Authors: *S. QIU, R. CAO, N. HERZ;
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Abstract: Episodic memory impairments are common in depression, yet the cognitive processes underlying these deficits remain poorly understood. The temporal context model predicts that successful episodic retrieval depends on reinstating temporal context, leading to organized recall of temporally neighboring items. We tested whether depression selectively disrupts temporal organization during memory retrieval. We analyzed free recall data from 133 epilepsy patients undergoing intracranial EEG monitoring who completed the Beck Depression Inventory (BDI). Participants completed either a free recall task involving unrelated word lists (n = 88) or a categorized free recall task (n = 91). Temporal and semantic clustering scores were computed for each recall list, and linear mixed-effects models examined the relationship between depression severity and memory organization while controlling for age, IQ, recall performance, and task type. Higher BDI scores were associated with reduced temporal clustering across tasks ($\beta = -0.0017$ per BDI point, $\chi^2(1) = 5.87$, $p = .015$), indicating diminished organization of recall according to temporal context. In contrast, depression severity was not associated with semantic clustering in either task ($p = .488$). These findings suggest a disrupted temporal context as a candidate cognitive mechanism underlying memory dysfunction in depression. Ongoing intracranial EEG analyses in 53 patients with hippocampal electrodes are testing whether reduced temporal clustering in depression reflects altered formation, maintenance, or reinstatement of hippocampal context representations.

Disclosures: S. Qiu: None. **R. Cao:** None. **N. Herz:** None.

Poster

PSTR335: Human Navigation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR335.01/LL44

Topic: I.09. Spatial Navigation

Support: T32 Grant T32MH119049
National Science Foundation IIS202-4633

Title: Distinct navigation strategies and entorhinal correlates of human path integration in immersive virtual reality

Authors: *A. S. TU[1], N. KROHN[1], M. J. STARRETT AMBROSE[4], C. E. STARK[2], M. HEGARTY[5], E. R. CHRASTIL[3];
[2]Neurobio. and Behavior, [3]Neurobio. & Behavior, [1]Univ. of California, Irvine, Irvine, CA; [4]Neurobio. & Behavior, UC Irvine, Irvine, CA; [5]Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Successful navigation relies on continuously updating one's position and orientation in space using self-motion cues (path integration), yet performance varies widely across

individuals. This variability likely reflects differences in strategy use and neural computations, such as metric processing supported by the entorhinal cortex (EC). Although EC grid cells are thought to provide a coordinate system for navigation, it remains unclear how EC grid-like signals measured with fMRI relate to path integration ability and whether this relationship depends on task demands and strategy use. To address these questions, 67 healthy young adults completed 2 immersive, walking path integration tasks in a virtual desert environment: Triangle Completion and Loop Closure. Triangle Completion requires participants to return to the start after walking 2 straight-line path segments, whereas Loop Closure requires them to indicate when they think they have returned to the start while walking a circular path. Participants reported the strategy used in each task, later categorized as either configural (integrating multiple paths into a structured representation) or homing (continuously updating a vector to the home location). In another session, participants underwent fMRI scanning while viewing a passive navigation video depicting movement through a large virtual room. This task elicited EC grid-like activity, measured as the strength of the 6-fold rotational symmetry in BOLD responses by travel direction. EC cortical thickness was also measured to assess how EC structure relates to path integration ability. Analyses revealed dissociable relationships between EC grid-like signals and performance across tasks: grid-like signals correlated with Loop performance, but not Triangle, suggesting a task-dependent role of the EC in path integration. This relationship also varied by performance level, with significant grid-like signals found only in less-able Triangle performers and more-able Loop performers. Together with differences in strategy use across tasks, these findings suggest that strategy moderates the relationship between EC grid-like coding and path integration ability. In planned additional analyses, we expect grid-like coding to relate more strongly to performance in those who rely on configural strategies. Also, by considering EC structure, we will evaluate how anatomical variation may contribute to navigation differences. Overall, this study highlights how differences in encoding and use of spatial information via distinct strategies may shape how traveled paths are stored and retrieved, providing insight into the mechanisms of navigation.

Disclosures: A.S. Tu: None. **N. Krohn:** None. **M.J. Starrett Ambrose:** None. **C.E. Stark:** None. **M. Hegarty:** None. **E.R. Chrastil:** None.

Poster

PSTR335: Human Navigation

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Program #/Poster #: PSTR335.02/LL45

Topic: I.09. Spatial Navigation

Support: NIH Grant R01NS135850
NIH Grant L70NS145340
NIH Grant F32NS129626

Title: Neural correlates of trial-by-trial reference frame switching during spatial memory recall

Authors: *M. J. STARRETT AMBROSE, C. E. STARK, E. R. CHRASTIL;
Neurobio. and Behavior, UC Irvine, Irvine, CA

Abstract: Long-standing models of spatial processing posit that retrosplenial cortex (RSC) is crucial for spatial transformations across viewpoint-dependent (egocentric) and observer-independent (allocentric) frames. In such models, changes to the relative utility of the egocentric or allocentric frame should result in either lower precision to maintain response speed or slower responding to maintain precision, but this prediction has not been directly tested. In previous behavioral work, we demonstrated that participants were similarly accurate but required more processing time to respond to spatial memory trials only when switching from an egocentric to allocentric reference frame. Here, we used a version of the same spatial memory stay-switch paradigm, adapted for functional magnetic resonance imaging (fMRI), where participants recalled information about spatial relationships from both egocentric and allocentric reference frames. Participants first learned the layout of stores in a virtual neighborhood and were told their memory would be tested by completing randomized trials from two spatial memory tasks. On egocentric trials, participants viewed a single store in a virtual desert and had to turn to face a second invisible target store. On allocentric trials, participants saw an aerial view of the circular desert and rotated a pointer to face the target. Critically, we systematically manipulated how often reference frames were repeated or switched. Calibration trials for both egocentric and allocentric trials were included as controls for univariate fMRI contrasts. Data from healthy young adults were analyzed to compare cognitive costs associated with reference frame switching. The primary dependent measures were memory accuracy (absolute angular error) and response time (from trial onset to response submission). Preliminary neuroimaging results show task-related activity in posteromedial brain regions that differed qualitatively across egocentric and allocentric trials. These results provide some of the first data showing how spatial memory networks reconfigure based on optimal reference frame for spatial memory retrieval across short, trial-by-trial, timescales.

Disclosures: M.J. Starrett Ambrose: None. **C.E. Stark:** None. **E.R. Chrastil:** None.

Poster

PSTR335: Human Navigation

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: I.09. Spatial Navigation

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BMBF 01GQ1705A
BMBF 01GQ2402A
NIH/NINDS U01 NS113198-01
DFG MO 930/4-2, MO 930/15-1, SFB 1089, SPP 2205, SPP 2411
ERC 101001121

Title: Concept cells guide human goal-directed navigation

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Abstract: Human spatial navigation is often guided by semantic information, e.g., objects or people that mark destinations. Regions of the medial temporal lobe (MTL) are critical for both memory and navigation. Importantly, the human MTL also contains concept cells—neurons that respond selectively and invariantly to specific objects or people. We therefore hypothesized that concept cells represent goal identities during memory-guided, goal-directed navigation. To test this idea, we recorded more than 2,400 neurons in epilepsy patients performing a navigation task in a virtual museum. On each trial, participants were cued with a sequence of images and words that, in a pre-task screening, had been identified as the preferred stimuli of recorded concept cells. Participants then located the cued images within the museum in the correct order. During planning, concept cell activity prospectively encoded upcoming goals and predicted successful navigation. During navigation toward a preferred goal, concept cells fired even before the goal came into view, and goal-specific activity predicted successful navigation. Once a goal was reached and therefore no longer held in memory, the corresponding concept cells returned to baseline. Together, these findings suggest that concept cells dynamically represent goal identity during human goal-directed navigation, from planning to navigation.

Disclosures: T. Guth: None. **I. Weichert:** None. **P. Büchel:** None. **P.C. Reinacher:** None. **A. Brandt:** None. **M.F. Khazali:** None. **A. Schulze-Bonhage:** None. **V. Borger:** None. **M.S. Kehl:** None. **R. Surges:** None. **B. Staresina:** None. **F. Mormann:** None. **L. Kunz:** None.

Poster

PSTR335: Human Navigation

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NIMH R01MH119086

Title: Transformations of cognitive maps for sensorimotor control

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Abstract: Embodied behavior involves transforming structured knowledge about the relationship between environment and action into motor signals, but how these transformations are coordinated across brain networks remains unknown. Participants learned associations between visual cues and isometric exertions that varied in force and duration, forming a two-dimensional cognitive map of a force-time space. During behavior, this force-time space was expressed in cortical regions using grid-like coding schemes, indicating a cognitive map of sensorimotor features. However, these representations diverged across brain regions. While the primary motor cortex encoded an endogenous force-time space distorted by perceived effort during motor execution, mnemonic regions maintained an unwarped, task-relevant representation. Dynamic causal modeling showed inhibitory motor-to-mnemonic coupling that predicted the transformation of endogenous effort-weighted motor signals into task-relevant sensorimotor maps which provided structured knowledge of cue-exertion associations. Furthermore, individual differences in learning and navigating the force-time space, as well as perceived effort during exertions, independently shaped mnemonic-to-motor coupling and mnemonic map geometry. These findings demonstrate that sensorimotor cognitive maps emerge from dynamic interactions between motor and mnemonic systems and are shaped by individual differences during the learning and execution of movement.

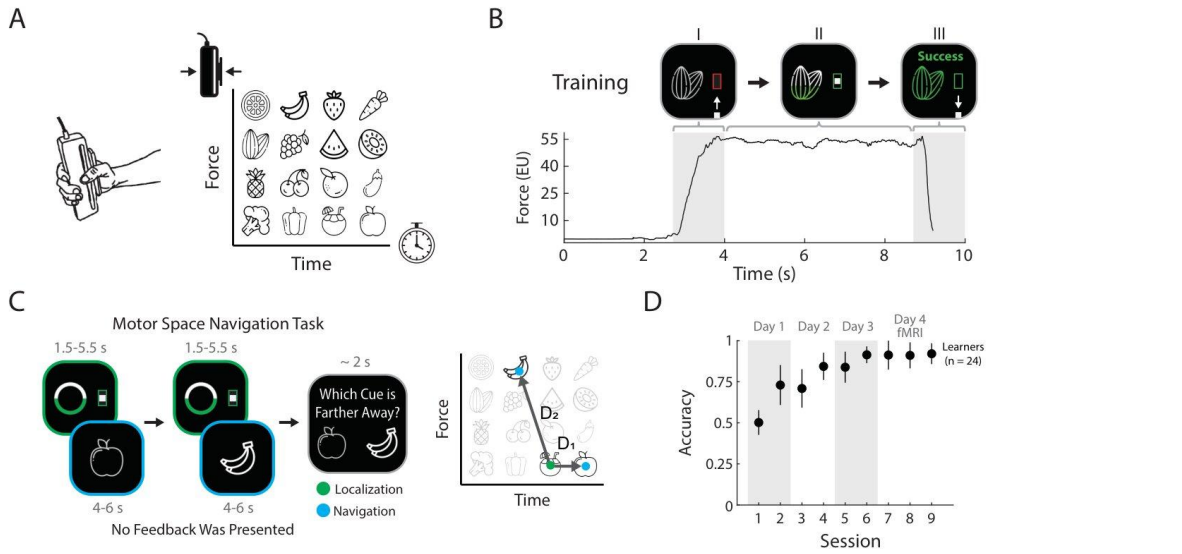


Figure 1: Participants associated effortful isometric exertions with external cues

(A) During training, participants performed isometric exertions using a hand dynamometer (left). They associated the force (intensity) and time (duration) of each exertion with a visual cue. The visual cues were arranged in a 4x4 grid-like force-time space (right), with four levels of force and time, respectively.
(B) For every trial in the training phase, participants initially performed an isometric exertion to guide a cursor to the target box (Panel I). Once reaching the target, the cue began to fill in green color and participants had to continue exerting at the target force level (Panel II). When the cue finished filling, participants let go of the hand dynamometer, and the cursor returned to baseline (Panel III). A force trace from a representative participant (Bottom panel). Force units were assigned as effort units (EU), where an EU of n corresponded to n% of the participant's maximum voluntary contraction (MVC).
(C) During the motor space navigation (MSN) task, participants completed two segments: 1) localization and 2) navigation. During localization, participants performed an isometric exertion like those during training (B), but the cue was hidden and replaced with a circle. Participants had to identify the cue that matched the exerted force and time level (green). During navigation, a target cue appeared, and participants had to compute the distances (T1, T2) between the hidden cue and the target cue in the force time space (blue). Finally, participants decided which target cue was farther from the hidden cue in the force-time space (T1 vs T2).
(D) Participants' mean performance in the MSN task across the four experimental days. Sessions 1-6 were throughout days 1-3. Participants who displayed greater than 80% accuracy on session 6 (n = 24) performed sessions 7-9 in the fMRI scanner. Error bars represent one std.

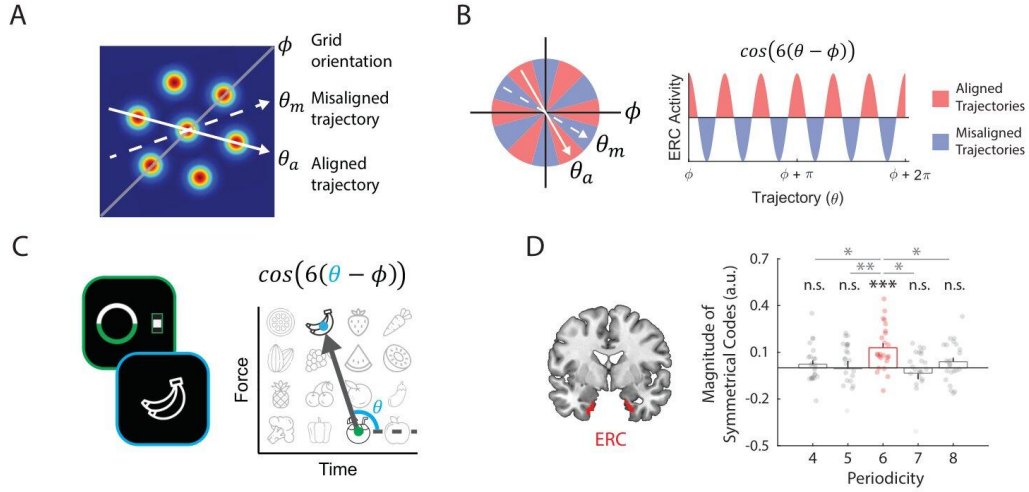


Figure 3: The entorhinal cortex utilizes grid-like codes to represent sensorimotor information

(A) Receptive fields of grid cells in the entorhinal cortex (ERC) are arranged hexagonally, resulting in different activity depending on the trajectory. Trajectories are categorized as aligned (θa) or misaligned (θm) with the grid orientation (ϕ).
(B) ERC activity as a function of trajectory can be modeled as a 6-fold cosine waveform where aligned trajectories pass through more receptive fields and evoke greater activity than misaligned trajectories.
(C) During the MSN task, the inferred trajectory, for each trial, was computed and adjusted by each participant's estimated grid orientation as they traveled from the localized cue (green) to the target cue (blue) in the navigation segment.
(D) ERC (anatomical mask in red) activity was significantly correlated with 6-fold modulation (*** $P < 0.001$; two-tailed one-sample Wilcoxon signed-rank test, corrected for number of periodicities (n = 5) using the Holm-Bonferroni method), but not with control periodicities (4,5,7,8 fold, all $P > 0.05$). Six-fold modulation signals in the ERC were also significantly greater than those of control periodicities (** $P < 0.01$, * $P < 0.05$; two-tailed paired Wilcoxon signed-rank test, corrected for number of comparisons (n = 4) using Holm-Bonferroni method). Error bars represent standard error (s.e.).

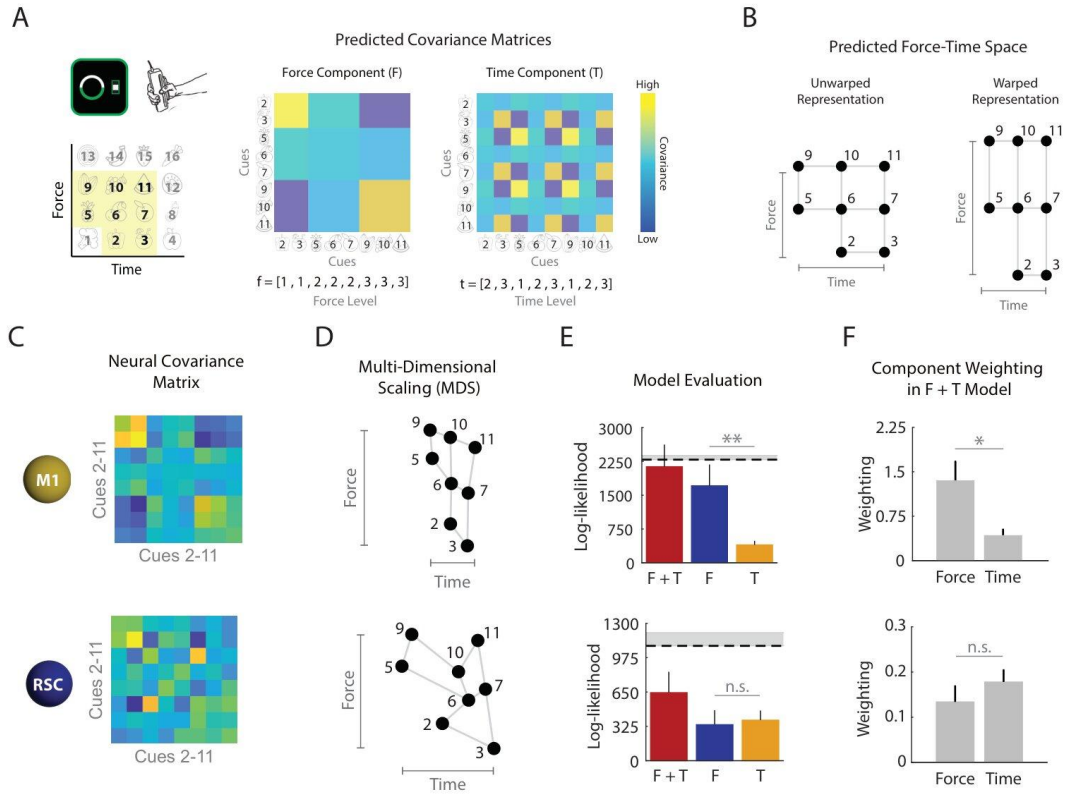


Figure 3: Sensorimotor and mnemonic regions differentially represent the force and time of exertions

(A) Pattern component modeling (PCM) analysis was performed to understand how different brain regions represent the force and time of exertion during the localization condition. The PCM analysis included exertion data from 8 cues (yellow box, numbered for cues 2-11) as those cues were sampled most frequently in the MSN task. Force (f) and time (t) feature sets were computed that defined the cues based on their respective force and time levels. These feature sets were used to compute predicted covariance matrices that described the covariance of a pair of cues due to either differences in force or time levels.
(B) Predicted force-time space from the sampled cues 2-11 that depicts an unbiased representation (left), where force and time features are equally represented, and a warped representation (right), where the cues are represented more saliently in force compared to time features.
(C) PCM results for M1 (top) and RSC (bottom). The cross-validated estimates of the neural second moment matrix describe the activity profile distribution for each brain region when exerting cues 2-11.
(D) Multi-Dimensional Scaling was performed (middle column), where the eight cues were projected on the eigenvectors of the neural covariance matrix for each representative brain region.
(E) The performance of each model (right column) for predicting the neural second moment matrix. The force (F) and time (T) models predicted the neural second moment matrices using both F and T models. The force and time (F + T) model utilized both components. The dotted line represents the lower bound noise ceiling. Error bars represent SEM. ** $P < 0.01$; two-tailed paired Wilcoxon signed-rank test, corrected for number of sensorimotor brain regions (n = 3) using Holm-Bonferroni method.
(F) The weights associated with the force and time components in the F + T model. The force component was weighted significantly greater than the time component for M1. * $P < 0.05$; two-tailed paired Wilcoxon signed-rank test, corrected for number of sensorimotor brain regions (n = 3) using Holm-Bonferroni method.

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Poster

PSTR335: Human Navigation

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Ford University Research Program
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Title: Voxelwise encoding model-based high-throughput hypothesis testing in naturalistic neuroimaging experiments

Authors: *T. ZHANG, J. L. GALLANT;
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Abstract: Hypothesis-driven experiments have been instrumental in analyzing neuroimaging studies of the human brain and have revealed many of its functional properties. However, hypothesis-driven studies typically examine representations in isolation, making it difficult to compare representations within the same setting, to explore high-dimensional representations in complex tasks, or to discover novel representations not conceived of during experiment design. The voxelwise encoding model (VEM) framework is designed to overcome all these challenges. However, the VEM framework is oriented toward prediction accuracy; to date, it has been difficult to directly compare VEM results, particularly those using many feature spaces, with results from classical point-null hypothesis testing experiments. To overcome this challenge, we extend the VEM framework to enable hypothesis testing with the fit models, providing a means to directly compare results of encoding model studies with those obtained by point-null hypothesis testing. In this extended framework, hypotheses are captured by feature spaces, effect sizes are quantified by explained variance, and statistical significance is assessed with permutation tests. To validate this VEM-based hypothesis testing framework, we applied it to an active navigation experiment and tested 51 hypotheses drawn from the literature. Results show that while many of these hypotheses reached significance in a shared naturalistic setting, some did not, and the spatial extent of significant locations varies widely between hypotheses. In addition to significance, the VEM-based hypothesis testing framework also provides estimates of effect size for each hypothesis. During naturalistic navigation, effect sizes follow a long-tailed distribution dominated by perceptual and motor representations, while more abstract representations account for a smaller fraction of the total response variance. This distribution likely reflects the demands of active navigation: while cognitive representations likely encode relatively stable goals and plans, perception and action representations must continuously update to track the current environment and translate plans into concrete actions. This unified framework bridges between high-resolution voxelwise encoding models and classical point-hull hypothesis testing, enabling direct comparisons of many results across paradigms in a shared naturalistic experiment.

Disclosures: T. Zhang: None. **J.L. Gallant:** None.

Poster

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Topic: I.09. Spatial Navigation

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R01HD097619

Title: Engagement of premotor and parietal regions when navigating sensorimotor cognitive maps

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[5]Kavli Neurosci. Discovery Inst., Baltimore, MD

Abstract: Skilled behavior requires integrating sensorimotor experiences with environmental information to guide future actions. Recent work has suggested that these learned representations may be organized as a cognitive-map-like representation, allowing flexible navigation through sensorimotor space. Here, we investigated whether higher-order motor regions support navigation through these sensorimotor cognitive maps. Twenty-four participants learned associations between visual cues and isometric hand-grip exertions that varied systematically in force and time duration, forming a two-dimensional force-time space. Participants then underwent functional magnetic resonance imaging (fMRI) while performing a Motor Space Navigation (MSN) task. On each trial, participants first produced an isometric exertion without being shown the associated cue and inferred its identity from the learned force-time representation. They then mentally navigated from this inferred cue to visually presented target cues to make spatial judgments within the learned space. Preliminary fMRI results revealed greater activation in parietal and premotor regions during mental navigation than during isometric exertion, indicating recruitment of higher-order motor regions beyond movement execution. Greater Euclidean distance between the exerted and target cues was associated with increased activation in bilateral premotor area (PMA) and right supramarginal gyrus. Higher-performing participants exhibited stronger distance-related activation in right PMA, suggesting greater neural sensitivity to the learned sensorimotor geometry. Examining force and time dimensions separately revealed partially dissociable representations: increasing temporal distance preferentially recruited left PMA, whereas increasing force distance additionally recruited right PMA and superior and inferior parietal regions. These findings suggest that premotor and parietal regions support mental navigation through learned sensorimotor representations and that distinct premotor-parietal networks preferentially encode force and time dimensions within a learned sensorimotor space.

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Poster

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Topic: I.09. Spatial Navigation

Support: National Science Foundation IIS2024633

Title: Resting-State Functional Connectivity Predicts Individual Differences in Spatial Navigation Abilities

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Abstract: Individual differences in spatial navigation abilities are linked to variations in brain structure and function, yet how functional communication between regions relates to these differences remains unclear. Resting-state fMRI provides insight into intrinsic connectivity patterns and their relationship to behavior. The present work examines how resting-state brain connectivity relates to navigation performance in three fully immersive virtual reality tasks. First, in the loop closure task, participants are walked in a circular trajectory and they indicate when they thought they had completed a full circle; accuracy is assessed via absolute angular error. Next, in the dual solutions paradigm, participants are asked to navigate between objects and could either take a learned or novel route; strategy preference is quantified by the relative number of times they take a shortcut. Third, in the maze wayfinding task, participants are asked to navigate between objects within a time limit, following exploration of the maze; accuracy is measured as proportion of correct trials. Resting-state fMRI data was collected separately, in which participants stayed awake and let their minds wander. We computed correlations of functional activity between brain regions, which we then compared with behavioral performance.To examine a priori hypotheses about navigation-relevant brain regions, we conducted ROI-to-ROI analyses, targeting the hippocampus, entorhinal cortex, parahippocampal cortex, retrosplenial cortex, medial prefrontal cortex, putamen, and caudate. We additionally applied connectome-based predictive modeling (CPM) with 10-fold cross validation to test whether whole-brain connectivity patterns could predict navigation performance in held-out subjects. Results revealed distinct connectivity profiles across the three tasks. ROI-level analyses demonstrated that functional connectivity between navigation related-regions, hippocampal, entorhinal, parahippocampal, and striatal regions, was related to performance. CPM successfully predicted individual differences in loop closure performance, but not maze wayfinding or strategy preference. These results provide insight into how neural connectivity supports individual differences in navigation and spatial decision-making.

Disclosures: N. Kaushik: None. **M. Hilal:** None. **M. Hegarty:** None. **E.R. Chrastil:** None.

Poster

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Support: Wellcome Principal Research Fellowship 222457/Z/21/Z
UKRI Frontier Research Grant EP/X023060/1

Title: Human hippocampal theta phase precession of button pressing during memory-guided navigation

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Abstract: The hippocampal local field potential is dominated by 4 - 12 Hz theta oscillations during memory function and translational movement. In addition, recent evidence suggests that rodent hippocampal theta oscillations synchronise with motor output during memory-guided behaviour. Here, we examined the relationship between the hippocampal theta rhythm and button pressing while human participants performed an abstract navigation task inside the MEG scanner. Specifically, we asked participants to traverse the shortest possible path between a given start and goal location either from memory, or by making a sequence of visually guided button presses presented on the screen. We found evidence for theta rhythmicity in button press timing during memory-guided, but not visually guided, navigation. Moreover, we found a negative circular-linear correlation between source reconstructed instantaneous hippocampal theta phases at each button press and proximity to the goal location during memory-guided, but not visually guided, navigation. This indicates phase precession of button pressing relative to hippocampal theta oscillations as a hidden goal location is approached during memory-guided navigation. Importantly, both the behavioural rhythmicity and phase precession of button pressing were replicated across two separate MEG experiments and modulated by task performance and experience. These findings are consistent with hippocampal theta sequences terminating earlier in each cycle as the distance to a hidden goal becomes shorter and suggest that the human hippocampal theta rhythm organises motor output during memory-guided navigation.

Disclosures: D. Wang: None. **Z. Huang:** None. **J.A. Bisby:** None. **N. Burgess:** None. **D. Bush:** None.

Poster

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NIH Grant R01EY031286

Title: Neural mechanisms underlying spatial reorientation in humans

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Univ. of Pennsylvania, Philadelphia, PA

Abstract: Spatial reorientation—the process of recovering one's bearings after becoming lost or disoriented—has been studied in many species. Despite an extensive behavioral literature, which has been highly influential in cognitive science (Gallistel, 1990; Hermer & Spelke, 1994), the neural mechanisms underlying spatial reorientation are not well understood. According to one formulation (Julian et al., 2018), spatial reorientation involves at least two components: recovery of the identity of the spatial environment (context retrieval) and recovery of one's position and directional orientation within that environment (location+heading retrieval). To identify the neural systems underlying these components, we implemented a dynamic navigation paradigm in which the demands on each component were systematically varied across individual reorientation events. Healthy human participants were scanned with fMRI while navigating through a virtual environment consisting of two connected chambers and traveling to the remembered locations of objects. En route to each goal location, they would occasionally experience brief interruptions in navigation: a gray screen would appear for 1.5 s, after which participants either found themselves at a different location (reorientation event) or at the same location with the same heading (non-reorientation event). In two scan runs, participants exclusively navigated a single chamber; in two subsequent runs, they navigated both chambers. Three conditions were thus compared: non-reorientation, single-environment reorientation, and dual-environment reorientation. We focused our initial analyses on brain regions involved in scene perception (Epstein & Baker, 2019) and place memory (Steel et al., 2021). Univariate analyses revealed greater retrosplenial complex (RSC) activation during reorientation conditions relative to non-reorientation conditions, consistent with RSC's established role in retrieval of spatial maps. Trial-wise coactivation analyses showed that, relative to non-reorientation events, reorientation increased functional coupling between ventral place-selective regions and the dorsal place-selective regions including RSC. Moreover, dual-environment reorientation selectively enhanced RSC connectivity with dorsal place-selective areas compared with single-environment reorientation, suggesting that RSC supports context retrieval by integrating and disambiguating spatially distinct environments. Together, these results reveal how place-selective regions are differentially recruited across the cognitive components of dynamic spatial reorientation.

Disclosures: L. Han: None. **R.A. Epstein:** None.

Poster

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BMBF 01GQ1705A
BMBF 01GQ2402A
NIH/NINDS U01 NS113198-01
DFG MO 930/4-2, MO 930/15-1, SFB 1089, SPP 2205, SPP 2411
ERC 101001121

Title: Investigating Spatial View Cells in the Human Temporal Lobe

Authors: *I. WEICHERT[1], T. GUTH[1], R. SOMANI[1], P. BÜCHEL[1], M. F. KHAZALI[3], P. C. REINACHER[5], A. SCHULZE-BONHAGE[4], A. BRANDT[4], V. BORGER[2], R. SURGES[1], F. MORMANN[1], L. KUNZ[1];
[1]Epileptology, [2]Neurosurg., Univ. Hosp. Bonn, Bonn, Germany; [3]Neurozentrum, [4]Univ. of Freiburg, Freiburg, Germany; [5]Dept. of Stereotactic and Functional Neurosur, Freiburg, Germany

Abstract: Multiple cell types have been implicated in spatial navigation, allowing us to interact with the world and memorize the spaces around us. Most prominently, place cells have been established in rodents and other animals, including evidence for place-like cells in the human brain through intracranial recordings in epilepsy patients. Studies in monkeys, however, have also focused on a different cell type, termed spatial view cells. Unlike place cells, which code for the position that is occupied, spatial view cells show activity in response to the space that is looked at, irrespective of the subject's location. Here, to investigate spatial view cells in humans, we performed human single-unit recordings with concurrent eye tracking during a virtual navigation task (12 participants). In this task, participants learned positions of objects in a virtual environment and later navigated to them during retrieval. We recorded single- and multi-unit activity from major medial temporal lobe regions, including the hippocampus, entorhinal cortex, amygdala, and parahippocampal cortex (about 2,000 units). We quantified whether the neurons' firing rates were modulated by the participants' 3D gaze position in the virtual environment. In our preliminary results, we find that about 15% of the recorded neurons are modulated by spatial view, and that these neurons are most prevalent in the parahippocampal cortex. In ongoing analyses, we investigate the overlap between spatial view cells and other cell types, including spatially and directionally modulated neurons. Together, this work helps identify the prevalence of spatial view cells in the human brain and disentangle their overlap with other functional cell types in the human medial temporal lobe.

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Poster

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Support: Deutsche Forschungsgemeinschaft (DFG); project id: 425899996 – SFB 1436

Title: The role of movement speed in human spatial representations

Authors: *V. REISNER[1], V. SEGEN[1,2], T. WOLBERS[1,2];
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Abstract: Path integration (PI) enables organisms to update their position estimate from self-motion. Entorhinal grid cells provide a candidate metric code for PI, and computational models suggest that their regularly repeating firing fields can arise from PI-based mechanisms. Critically, these models require directional and speed-related inputs to update grid activity according to movement. Electrophysiological studies have identified speed-sensitive signals that coexist with grid cells in the rodent medial entorhinal cortex, and altered speed coding has been linked to disrupted grid-cell periodicity in disease models. Yet how macroscopic speed-related signals are represented during human navigation, and how they relate to entorhinal grid-like coding, remains unclear. We used fMRI to investigate these questions in healthy young adults completing two virtual reality-based tasks. In a passive linear PI task, participants experienced translations at four speed levels and at the end of each movement phase estimated the traveled distance, allowing us to probe the behavioral and neural signatures of movement speed. In a separate spatial memory task, participants encoded locations during passive navigation, allowing the assessment of grid-like BOLD signals. Linear-PI results revealed meaningful but compressed distance estimation across speed levels. Neuroimaging analyses indicated regionally distinct univariate speed modulation and multivariate representational similarity patterns that scaled with movement speed, suggesting that visual motion-sensitive and entorhinal regions represent self-motion information in different formats. In the spatial memory task, we observed 6-fold grid-like BOLD modulation in the entorhinal cortex. We further related individual differences in speed sensitivity from the linear PI task to the strength of grid-like signals in the spatial memory task, providing a cross-task assessment of self-motion coding and grid-like representations. Together, these findings suggest that human navigation engages distinct, potentially interacting components for speed-related self-motion processing and entorhinal grid-like spatial coding.

Disclosures: V. Reisner: None. **V. Segen:** None. **T. Wolbers:** None.

Poster

PSTR335: Human Navigation

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Dr. Miriam and Sheldon G. Adelson Center for the Biology of Addictive Diseases, Grant number 601133461

Title: Divergent spatial strategies and acquisition rate in a cross-species T-maze

Authors: T. LOUSHY KAY[1], L. BIKOVSKI[2], E. BEEN[4], ***C. PICK**[3];
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Abstract: Background: Spatial navigation relies on allocentric (map-like) and egocentric (body-centered) strategies, yet the extent to which these processes are conserved across species remains unclear. We aimed to compare learning speed, strategy preferences, and performance in mice and humans using translationally analogous T-maze tasks.**Methods:** Mice (n=24) performed a physical T-maze, while humans (n=62) navigated a virtual reality analogue version with natural locomotion. Both underwent learning and probe phases to isolate Response (egocentric), Cue, and Place (allocentric) strategies. Human data included self-reports and eye-tracking measures for validation and further understanding of the underlying cognitive processes.**Results:** Humans learned ~10-fold faster than mice ($P<0.001$). Multivariate analysis revealed strong species differences in strategy use ($P<0.001$): Mice relied more heavily on the Response strategy, whereas humans exhibited a stronger preference for the Cue strategy. Humans also demonstrated greater Place consistency ($P<0.001$). No significant sex or species-by-sex interaction was found. Human behavioural measures converged with self-reports ($P<0.001$).**Conclusions:** These findings reveal conserved navigational abilities across mammals but pronounced species-specific preferences. Mice rely on egocentric strategy, while humans exhibit faster learning and more versatile navigation, integrating landmark-based strategies. This highlights a significant evolutionary divergence in spatial cognitive strategies despite broadly conserved hippocampal architecture.

Disclosures: T. Loushy Kay: None. **L. Bikovski:** None. **E. Been:** None. **C. Pick:** None.

Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.01/LL56

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

Support: 1R01DA055823

Title: Single Nucleus Spatiomolecular Profiling of the Human Habenula

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Abstract: The habenula (Hb) is a bilateral midline structure critical for reward processing and mood regulation. Dysfunction of the Hb is associated with several neuropsychiatric disorders, including major depressive disorder (MDD), schizophrenia, and substance use disorders (SUDs). The Hb is composed of two distinct subregions: the medial habenula (MHb) and the lateral habenula (LHb), which have unique cell types, connectivity, and functions. Due to its small size, few studies have investigated the molecular anatomy of the human Hb and little is known about the transcriptomic and epigenetic signatures of spatially organized LHb and MHb cell types or their cell-to-cell communication. Here we sought to generate a high resolution spatiomolecular map of the human Hb using spatial transcriptomics and single nucleus RNA-sequencing combined with ATAC-sequencing . Using the Multi-ome assay (10x Genomics), we measured gene expression and chromatin accessibility in individual nuclei across Hb cell types from 10 adult neurotypical control donors (7 male, 3 female; 62,950 nuclei). We identified LHb, MHb, glial, and ependymal subpopulations and defined cell-type specific regulatory relationships between transcription factors, target genes, and open chromatin regions linked to gene expression. We performed VisiumHD (10x Genomics) on a subset of these donors (n=10 tissue sections from 5 donors) and identified the spatial location of molecularly distinct LHb cell types, including 2 subpopulations expressing inhibitory neuron marker genes located at the lateral border of the LHb. Using LIANA+ and CRAWDAD, we performed cell-cell communication analysis and defined cell type relationships between Hb neurons and astrocytes as well as ligand-receptor interactions between LHb and MHb neurons. We integrated single cell and spatial data with genome wide association studies (GWAS) of MDD and SUDs to identify Hb cell types and spatial domains enriched in genes associated with risk for neuropsychiatric disorders. Additionally, we present interactive web resources to explore these single nucleus and spatial datasets. Together, we present a landmark molecular neuroanatomical atlas of the human Hb and provide novel insights into how genes associated with psychiatric disorders and addiction map to Hb subregions and cell types.

Disclosures: K.D. Montgomery: None. **S.V. Bach:** None. **A. Chandra:** None. **R. Zhang:** None. **S.E. Maguire:** None. **H. Divecha:** None. **R. Bharadwaj:** None. **J.E. Kleinman:** None. **T.M. Hyde:** None. **K.R. Maynard:** None.

Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.02/LL57

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

Support: NIDA Grant DA055823

Title: Transcriptomic and genetic dissection of the human habenula in depression and opioid use disorder

Authors: *J. WERNER[1], K. MONTGOMERY[1], I. DEL ROSARIO[1], M. BARSE[1], S. V. BACH[1], N. EAGLES[1], A. CHANDRA[1], R. ZHANG[1], G. PERTEA[1], S. MAGUIRE[1], R. MILLER[1], R. BHARADWAJ[1], A. DEEP-SOBOSLAY[1], J. E. KLEINMAN[1,2], T. M. HYDE[1,2,3], L. COLLADO TORRES[1,5,6], K. R. MAYNARD[1,2,4];
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Abstract: The habenula is a key hub of reward circuitry that modulates dopaminergic, serotonergic, and noradrenergic signaling and has been implicated in major depressive disorder (MDD) and opioid use disorder (OUD). Elevated habenula activity is associated with depression, while interventions that modulate habenula activity, including ketamine and deep-brain stimulation, can produce antidepressant effects in treatment-resistant patients. The habenula is also highly enriched for expression of the mu opioid receptor, OPRM1, and habenular dysfunction has likewise been implicated in OUD. Despite these associations with neuropsychiatric disease, the human habenula remains poorly characterized at the molecular level, particularly in disease contexts, as its small size and midline location make it difficult to isolate for molecular profiling in postmortem tissue. To address this gap, we first constructed a single-nucleus RNA-sequencing (snRNA-seq) atlas of the postmortem human habenula from 10 neurotypical adult donors, anchored on evolutionarily conserved cell-types shared across zebrafish, mouse, and human. We then leveraged these conserved cell-type profiles to perform a transcriptional and genetic dissection of the human habenula in MDD and OUD. We generated a large-scale snRNA-seq dataset of the human habenula (739,608 nuclei) from neurotypical controls, individuals with MDD, and individuals with comorbid MDD+OUD (n = 20 donors per group), coupled with SNP-array genotyping. To identify diagnosis-sensitive cellular populations and molecular programs, we performed cell type-specific differential expression analyses, transcriptional decomposition of healthy and disease states using non-negative matrix factorization, and genetic mapping of MDD and OUD risk through expression quantitative trait loci (eQTL) and risk-variant enrichment analyses. We identified cell type-specific expression associated with MDD and OUD, as well as cell type-specific eQTL expression of genome-wide association study (GWAS) risk variants for these disorders. Altogether, this study provides a large-scale, cell type-resolved molecular characterization of the human habenula in neuropsychiatric disease, establishing a framework for linking genetic risk to disease-associated cellular states within a central node of reward circuitry.

Disclosures: J. Werner: None. **K. Montgomery:** None. **I. Del Rosario:** None. **M. Barse:** None. **S.V. Bach:** None. **N. Eagles:** None. **A. Chandra:** None. **R. Zhang:** None. **G. Pertea:** None. **S. Maguire:** None. **R. Miller:** None. **R. Bharadwaj:** None. **A. Deep-Soboslay:** None. **J.E. Kleinman:** None. **T.M. Hyde:** None. **L. Collado Torres:** None. **K.R. Maynard:** None.

Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.03/LL58

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

Support: NIH Grant 5R21DA060407
NIH Grant 1R01DA065276

Title: Characterization of opioid-induced gene expression in discrete habenula cell types and projection neurons

Authors: *J. KIM[1], R. MAGNARD[2], B. A. OSTER[3], F. R. M. SIEWE[1], M. BARSE[1], J. M. WERNER[1], J. J. REHG[1], S. E. MAGUIRE[1], R. A. MILLER[1], E. A. YALCINBAS[1], E. CHALOUX-PINETTE[2], K. D. MONTGOMERY[1], M. MAYEN QUIROZ[1], J. MIRANDA-BARRIENTOS[1], P. H. JANAK[2], L. COLLADO TORRES[1], K. R. MAYNARD[1];
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Abstract: The opioid epidemic is a significant public health crisis requiring accelerated efforts to translate mechanistic studies into therapeutic developments. Substance use disorders feature dysregulation of brain reward circuits, especially dopaminergic systems governing motivated behavior. The habenula (Hb) is an “anti-reward” center that sends projections to the ventral tegmental area (VTA) and other aminergic centers to modulate reward seeking. Hb circuit dysfunction is associated with addiction, but the underlying molecular mechanisms, especially in the context of opioid use disorder (OUD), are unknown. Here, we generated single nucleus RNA-sequencing (snRNAseq) data from the rat Hb (n=6/sex/condition) following an extended fentanyl self-administration paradigm in which rats underwent 6 daily 2-hour short-access (ShA) acquisition sessions, which progressed to 18 daily 6-hour sessions long-access (LgA) sessions. Brains were collected 90 minutes after the final LgA session, after which neurons were enriched for molecular profiling using snRNAseq. In parallel, we also performed snRNAseq on Hb neurons projecting to the VTA (Hb-VTA) in mice to define circuit-specific molecular profiles. With the integrated datasets, we identified fentanyl-sensitive differentially expressed genes (DEGs) in Hb-VTA projection neurons, and gene expression changes correlated to self-administration behavioral measures such as total fentanyl intake across ShA and LgA sessions and average infusion rate during the drug loading phase, among others. We identified gene regulatory mechanisms that mediate cell type-specific fentanyl DEGs within evolutionarily conserved medial and lateral Hb clusters. Of these clusters, LHb.4 had the greatest number of DEGs, which were enriched for functions related to synaptic regulation and neuronal morphology in gene set enrichment analyses. We further integrated these findings with genome wide association studies of substance use disorders (SUDs) from human datasets and found that LHb.4 was most enriched for genetic risk for SUDs. Future work will integrate these findings with human single cell and spatial transcriptomics Hb datasets to map how populations associated with OUD risk and opioid response are topographically organized in the Hb.

Together, these findings will reveal transcriptomic signatures associated with opioid intake and risk for OUD in spatially discrete Hb cell types and circuits, which can inform future functional studies and help translate insights from rodent models into cell type- and circuit-based therapeutic strategies for OUD.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.04/LL59

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

Support: Swedish Research Council Grant 2023-02656
Alzheimerfonden Grant AF-1033516

Title: High resolution atlas of the human locus coeruleus

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Neurosci., Karolinska Inst., Solna, Sweden

Abstract: The locus coeruleus (LC) is a noradrenergic brainstem nucleus residing in the dorsal pons. As the primary source of noradrenergic (NA) innervation in the brain, the LC maintains an extensive projection network to cortical and subcortical regions regulating brain states such as arousal, attention, and wakefulness. The region is central in the pathophysiology of several diseases e.g., the LC is among the first brain structures to exhibit tau pathology related to Alzheimer's disease, decades before the manifestation of the first clinical symptoms. However, the molecular landscape, cellular organization, sexual dimorphism, and selective vulnerability of the human LC remain poorly understood. To characterize the spatial architecture of the human LC, we integrate spatial transcriptomics and single nucleus RNA sequencing (snRNAseq). Using high-resolution spatial transcriptomics (Stereo-seq) we analyzed over 1.5 billion spatial points (resolution 0.5 μm) covering 8 pons samples (age 77-88, non-demented, 4f:4m, and with a postmortem delay of <7h). Through unsupervised Leiden clustering of spatial bins (25 μm^2/bin) we identified 16 transcriptionally distinct spatial domains corresponding to anatomical regions such as the LC, vasculature, and serotonergic neurons. The analysis further revealed spatially heterogenous expression of genes within the LC and pons, such as of the neuropeptides *TAC1* and *CARTPT*, indicating spatial compartmentalization. The snRNAseq dataset is based on 42,657 isolated nuclei (n=2, age 77-81, postmortem delay <6h, 1f:1m) where 2,321 nuclei present with a neuronal profile. These neuronal nuclei include excitatory (n = 634, *SLC17A6*), inhibitory (n =

763, *GAD2*), and NA (n = 222, *TH*, *DBH*) neuronal populations. In the snRNAseq data 120 *TH* and 100 *DBH* counts were detected, while in the spatial data an average of 28942 *TH* and 62172 *DBH* counts were detected per sample. This striking increase in transcript recovery demonstrates that spatial transcriptomics significantly expands NA profile capture, justifying a multi-omic approach for the human pons and LC. Utilizing spatial binning, we comprehensively characterize high-resolution NA signatures and classify LC cell types, contributing to the Human Protein Atlas framework. Ultimately, this work defines the molecular boundaries of the human LC, resolving its cellular heterogeneity within its anatomical context.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

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Program #/Poster #: PSTR336.05/LL60

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

Support: R01DA053581
F32MH139150

Title: A multimodal, spatiomolecular atlas of the human lateral septum across neuroanatomical axes

Authors: *M. R. ABRAMSON[1], R. A. PHILLIPS, III[1], Y. DU[1], S. V. BACH[1], H. A. ALGRAIN[1], I. DEL ROSARIO[1], S. E. MAGUIRE[1], R. MILLER[1], M. D. ROMAC[2,3], J. E. KLEINMAN[1,4], T. M. HYDE[1,4,5], V. D. COSTA[2,3,8], S. C. HICKS[9,6,10,11], K. MARTINOWICH[1,4,7,12], S. C. PAGE[1,4];
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Abstract: The lateral septum (LS) is a predominantly GABAergic midline structure in the basal forebrain that exerts functional control over evolutionarily conserved behaviors, including sociability, aggression, maternal behavior, avoidance, and reward-seeking. In the rodent, the structure has been anatomically subdivided into transcriptionally distinct functional units with topographically organized innervation patterns along the dorso-ventral (DV) and rostral-caudal axes. Single-nucleus RNA sequencing (snRNA-seq) studies in our lab identified broad cross-

species conservation of LS transcriptional signatures between humans and mice. However, mapping the spatial organization of these cell populations in human tissue is technically challenging due to the distortion of septal neuroanatomy during standard post-mortem processing of human brains. With developed expertise in post-mortem human forebrain anatomy and standardized dissection procedures, and by leveraging cross-species molecular profiles, our team generated a detailed molecular atlas of the human LS and surrounding structures. Using multimodal spatiomolecular atlasing techniques, we sampled several morphologically preserved LS's across the anterior-posterior (AP) axis. We defined gene expression signatures for the canonical septal domains and provided novel characterization of the ventral subregion of the LS and the lambdoid septal (Ld) region. We identified neuronal heterogeneity among LS subpopulations, with spatial gradients in proportions across neuroanatomical axes, and shared molecular features between LS and other limbic regions. The data generated here will enable computational inference of the spatial localization of cellular identities in samples with suboptimal neuroanatomical presentation and in samples from other vertebrate species. As such, the atlas provides a crucial bridge to translating the molecular foundations of LS-mediated social and motivated behaviors from model species to humans.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

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Program #/Poster #: PSTR336.06/LL61

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

Support: 5R01MH117291-07

Title: Spatiomolecular organization of serotonergic neurons in the dorsal raphe nucleus of the human brain

Authors: *I. C. DEL ROSARIO[1], S. V. BACH[2], J. WERNER[3], R. MILLER[4], S. MAGUIRE[4], R. BHARADWAJ[4], J. E. KLEINMAN[6], T. M. HYDE[7], K. MARTINOWICH[5], K. R. MAYNARD[8];
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Sci., Lieber Inst. For Brain Develop., Washington, DC; [7]Genet. Neuropathology, Lieber Inst. For Brain Develop., Baltimore, MD; [8]Mol. Neuroanatomy, Lieber Inst., Baltimore, MD

Abstract: The dorsal raphe nucleus (DRN) is a bilateral, neurochemically heterogeneous complex situated in the midline of the brainstem extending rostro-caudally from the midbrain to the rostral pons. It is subdivided into five cytoarchitecturally distinct subnuclei: interfascicular (DRif), ventral (DRv), ventrolateral (DRvl), dorsal (DRd), and caudal (DRc). While the DRN contains a diversity of cell types, including GABA, glutamate, and dopamine populations, it is distinguished by the presence of serotonergic (5-HT) neurons, which serve as the brain's primary source of 5-HT. Single-nucleus RNA sequencing (snRNA-seq) studies in the mouse DRN revealed remarkable cellular heterogeneity, including 5 transcriptomically distinct 5-HT populations that had discrete spatial topography. However, an equivalent spatiomolecular data resource for the human DRN does not exist. These data are particularly consequential given that the DRN, along with the median raphe nucleus (MRN), plays a major role in mood regulation, emotional processing, and stress response. DRN dysregulation is implicated in several neuropsychiatric disorders, including major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). Moreover, selective serotonin reuptake inhibitors (SSRIs), the first-line pharmacological treatment for both disorders, act directly on DRN 5-HT neurons. Despite this clinical relevance, the spatial organization and molecular signatures of 5-HT neurons within the human DRN remain poorly understood. Additionally, it is unclear whether the cellular diversity of DRN cell types described in rodents is conserved in the human DRN. Here, we combined RNAscope single-molecule fluorescence in situ hybridization (smFISH) and Cresyl Violet staining to delineate the cytoarchitecture of the DRN in postmortem human tissue and map the distribution of 5-HT neurons across the rostro-caudal axis in eight neurotypical control donors. Our results reveal clear anatomical delineation and a unique bilateral serotonergic cell distribution pattern across the DRc, DRd, Drv, and DRif and the MRN. At the level of the midpons (Obex +30mm), we performed spatially resolved transcriptomics using the 10X Genomics Visium CytAssist HD platform to construct a spatial transcriptomic map of diverse DRN cell-type populations (n=8). We identified spatially organized 5-HT neurons and defined their molecular signatures. Characterizing distinct 5-HT subpopulations within the human DRN can support the development of novel therapeutic approaches and advance efforts towards precision treatment of psychiatric disorders involving 5-HT dysregulation, like MDD and PTSD.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.07/LL62

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

Title: Integration of Single Nuclei RNAseq Data into the HPA Brain Resource, a Comparison of Transcriptomic Profiles

Authors: E. SKARWAN[1], N. MITSIOS[1], E. HUSÉN[1], J. MULDER[1], ***E. SJOSTEDT**[2,3]; [1]Neurosci., [2]Karolinska Institutet, Solna, Sweden; [3]Protein Sci., The Royal Inst. of Technol., Solna, Sweden

Abstract: The Human Protein Atlas (HPA) Brain Resource contains transcriptomic profiles from anatomically well defined brain regions generated using micro dissected tissue samples and bulk RNA sequencing. To complement this data with cell type resolved information, a publicly available single nucleus RNA sequencing (snRNAseq) dataset has been integrated into the latest version of the resource (HPA v26, released November 11, 2026). Although the anatomical resolution and sampling strategies differ between the datasets, comparisons across corresponding major anatomical structures enabled evaluation of gene expression patterns at both subregional and cellular levels. The integrated resource allows users to explore gene expression across micro dissected brain regions alongside cell type specific profiles, providing additional biological context and facilitating interpretation of regional transcriptomic signatures. To enhance the cellular resolution, the snRNAseq dataset was reprocessed at the regional level and further stratified into neuronal and non-neuronal populations, with separate UMAP-based clustering analyses performed for each group. While a preliminary version of this data was previously available through the HPA Single Cell Resource, it has now been added to the Brain Resource, enabling a unified brain-centric view of the transcriptomic landscape. The expanded resource provides a hierarchical perspective on human brain transcriptomics, spanning multiple levels of biological organization: from whole-body comparisons, where brain expression can be contrasted with peripheral tissues using bulk RNAseq data from the HPA Tissue Resource; to regional variation captured through the micro dissected brain subregions; to local cellular environments represented by spatial transcriptomics data; and finally to cell type specific expression profiles derived from snRNAseq. Together, these complementary data modalities allow users to investigate gene expression across scales, from organs and brain regions to individual cell populations. This integration represents a significant extension of the HPA Brain Resource, bridging bulk and single cell transcriptomic data within a unified framework to support studies of human brain organization, cellular diversity, and function.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.08/LL63

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

Support: Swedish Research Council
Knut and Alice Wallenberg Foundation

Title: Integrating bulk with spatial transcriptomics to build a cellular and regional transcriptome atlas of the adult human brain

Authors: *N. MITSIOS[1], E. HUSÉN[1], E. SKARWAN[1], P. OKSVOLD[2], K. VON FEILITZEN[2], T. ZHENG[1], E. GERRITS[1], M. PALKOVITS[3], T. G. HOKFELT[1], E. SJOSTEDT[1], J. MULDER[1];
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Abstract: The Human Protein Atlas (HPA; www.proteinatlas.org) serves as a public online database that offers a comprehensive overview of protein expression and distribution in all primary human tissue types, including approximately 200 subregions of the human brain. This platform provides an extensive summary of gene and protein expression within the principal anatomical brain structures, by integrating in-house generated RNA sequencing and publicly available single-nucleus transcriptomic data with immunohistochemistry (IHC). With the recent advances in RNA-sequencing technologies, the field of high-resolution spatial transcriptomics (ST) has emerged as a powerful technique for studying single-cell transcriptomes in their spatial context, yielding essential tools for mapping the spatial distribution of mRNA transcripts within the brain. A major advantage of ST is its ability to associate gene and protein expression with specific cell types, even when protein distribution patterns lack morphological features for cell type identification by IHC. Previously, we had incorporated ST data, generated on the stereo-seq platform, to delineate the spatial patterns of gene expression across the principal cell types (neurons, astrocytes, oligodendrocytes, microglia and vascular cells) from several cortical and cerebellar tissue sections of the adult human brain. In the latest HPA release, launched in November 2026, we have substantially expanded both the scope and range of the spatial transcriptomics data, now including more anatomically distinct regions of the human brain (cerebral cortex, cerebellum, hippocampus, pons and spinal cord), thereby extending the brain coverage from two to five main regions. In addition, we have developed a new visualization framework that focuses on spatial niches within each region, enabling the identification and exploration of niche-specific expression patterns and local cellular microenvironments. By extracting spatial co-expression signatures, transcripts can be linked to major cell types while simultaneously revealing regional heterogeneity. All data presented is open access and freely available in the brain section of version 26 of the Human Protein Atlas (HPA26).

Disclosures: N. Mitsios: None. **E. Husén:** None. **E. Skarwan:** None. **P. Oksvold:** None. **K. von Feilitzen:** None. **T. Zheng:** None. **E. Gerrits:** None. **M. Palkovits:** None. **T.G. Hokfelt:** None. **E. Sjostedt:** None. **J. Mulder:** None.

Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.09/LL64

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

Title: The Mammalian RNA Atlas: Neural Gene Expression Patterns Across 90 Million Years of Species Divergence

Authors: *E. SKARWAN[1], N. MITSIOS[1], E. HUSÉN[1], J. MULDER[1], E. SJOSTEDT[1,2]; [1]Dept. of Neurosci., Karolinska Institutet, Solna, Sweden; [2]Protein Sci., KTH Royal Inst. of Technol., Stockholm, Sweden

Abstract: In addition to alterations in gene sequences, changes in gene expression play a central role in species divergence. While indispensable core genes face evolutionary pressure to maintain stable expression patterns and ensure ancestral physiological functions, divergent tissue expression profiles drive species-specific adaptation. Here, we investigate the regional specificity and distribution of protein-coding genes across brain regions to identify conserved or divergent expression profiles across species. We quantified and compared transcriptomic patterns of the human brain to those of the macaque, mouse, rat, and pig across multiple regions spanning the entire brain. Our study analyzes 12,888 protein-coding genes with uniquely matched 1:1 orthologs across all five species, along with an additional 3,027 human protein-coding genes that have a unique corresponding ortholog in at least one, but not all, of the other species. Preliminary comparative analysis indicates that, based on our definition of tissue enrichment, the brain exhibits the highest proportion of conserved tissue-enriched orthologous genes shared across all five species compared to other major organs in the body. More specifically, brain regions such as the cerebellum, medulla oblongata, hypothalamus, and basal ganglia show the highest degree of conservation, indicating a deeply ingrained constraint on their functional roles. Expression profiles for subregions, regional domains, and main brain regions, across the different species, are all available for exploration in the recently released Mammalian RNA atlas (www.rnaatlas.org/brain). Here, users can explore regional specificity across different species, compare for species overlap and conservation, as well as search for their favorite protein of interest. These results are part of a larger effort aiming to map the human and mammalian proteome in the light of evolution, presented under the framework of the Human Protein Atlas (HPA; www.proteinatlas.org) and the Mammalian RNA Atlas, with a major update and data addition for HPA v26 released on November 11th.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

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Program #/Poster #: PSTR336.10/LL65

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

Support: NIA grant R01AG085933

Title: Spatial Proteogenomic Mapping of Neuromelanin and Phosphorylated Tau Microenvironments in the Human Locus Coeruleus in Alzheimer's Disease.

Authors: *H. DIVECHA[1,2], M. TIPPANI[4], B. MULVEY[4], H. A. ALGRAIN[4], I. DEL ROSARIO[4], S. V. BACH[5,8], Y. DU[4], R. BHARADWAJ[4], J. MATTHIAS[9], S. MAGUIRE[4], S. KWON[6,3], R. MILLER[7], J. E. KLEINMAN[11,8], T. M. HYDE[12,10,8], S. HICKS[14,9,15], K. MARTINOWICH[4,2,8,15], S. C. PAGE[13,8], K. R. MAYNARD[16,2,8];
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Abstract: The locus coeruleus (LC) is a brainstem nucleus that serves as the primary source of norepinephrine (NE), and is among the first regions to degenerate in Alzheimer's disease (AD). LC neurons accumulate neuromelanin (NM), a dark pigment produced as a byproduct of catecholamine synthesis, until middle age, after which NM levels decline with further aging and in AD. The LC is the earliest site to accumulate phosphorylated tau (pTau), a hallmark of AD pathology. However, how NM burden within LC-NE neurons and pTau pathology in the surrounding microenvironment converge to drive LC vulnerability in AD is unknown. Therefore, we generated paired transcriptome-scale and protein-level spatial maps of the human LC in AD to link gene expression and NM content to pTau-defined cellular microenvironments.
We profiled fresh-frozen postmortem LC tissue from 30 elderly donors with high AD pathology. Following tissue dissection, LC inclusion was confirmed by histological staining and presence of canonical LC markers (TH, DBH, SLC6A2) using RNAscope single molecule fluorescence in situ hybridization. Adjacent tissue sections were assayed by Visium Spatial Proteogenomics (SPG), which paired whole-transcriptome capture at 55 μm resolution with multiplexed immunofluorescence (IF) for pTau (AT8), astrocytes (GFAP), microglia (TMEM119), and vasculature (Claudin-5). NM pigment was imaged in the same sections.
Following quality control, spots were spatially clustered to define LC and non-LC spatial domains and catalog resident cell types in these domains. Each 55 μm spot was also annotated by its pathology and microenvironment features (NM content and pTau, astrocyte, microglia and vascular signal). Differential expression across these microenvironment categories revealed transcriptional programs associated with pTau pathology and NM burden, nominating molecular correlates of LC-NE neuron vulnerability in AD. Together, these spatial maps help to disentangle the cell-intrinsic and microenvironmental drivers of LC degeneration in AD.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.11/LL66

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

Support: NIMH Grant R01MH126393
NIMH Grant R01MH123183
NIGMS Grant R35GM150671
Lieber Institute for Brain Development,

Title: Mapping spatially organized molecular and genetic signatures of schizophrenia across multiple scales in human prefrontal cortex

Authors: *S. KWON[1,2,3], B. GUO[6,7], C. FANG[6], M. TIPPANI[1], S. V. BACH[1,4], G. PERTEA[1], R. A. MILLER[1], S. E. MAGUIRE[1], A. IATROU[8,10,11], N. EAGLES[1], M. R. VALENTINE[1], S. OH[1], A. JAJOO[9], Y. DU[1], A. NGUYEN[1], R. ZHANG[1], U. KAIPA[1], H. DIVECHA[1,2], J. S. LOBANA[1], J. E. KLEINMAN[1,4], S. HAN[1], N. P. DASKALAKIS[8,10,11,12], T. M. HYDE[1,4,5], L. COLLADO TORRES[1,6,13], S. C. PAGE[1,4], K. R. MAYNARD[1,2,4], S. C. HICKS[6,13,14,15], K. MARTINOWICH[1,2,4,15];
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Abstract: The dorsolateral prefrontal cortex (dlPFC) is central to cognitive dysfunction in schizophrenia (SCZ), yet how molecular changes are organized across cortex remains unclear. Here, we applied complementary spatial transcriptomic approaches spanning laminar domains, microenvironments, and cell types in postmortem human dlPFC. At the laminar level, SCZ-associated transcriptional changes were strongest in glia-enriched domains (layer 1/meninges and white matter), including down-regulation of microglia-associated genes, whereas genetic risk localized to neuronal-rich gray matter. We next analyzed SCZ-linked microenvironments including neuropil, neuronal, perineuronal net, and vascular compartments. Within these, neuronal and synaptic transcriptional changes were most prominent in neuropil, showing down-regulation of activity-dependent synaptic genes and inhibitory neuron markers. At the cellular level, these signals reflected intrinsic alterations localized to cell types. Across analyses, patterns converged on altered BDNF-TrkB signaling and inhibitory circuit dysfunction. Together, our

findings highlight spatial scale as a key determinant in resolving neuronal and non-neuronal aspects of SCZ-associated biology.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.12/LL67

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

Title: Associations of Rare Variants with Depressive Symptoms in the Old Order Amish Founder Population

Authors: *Y. AHMED[1], E. HUMPHRIES[2], F. J. MCMAHON[3], P. KOCHUNOV[4], E. HONG[5], S. A. AMENT[6];
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Abstract: Founder populations such as the Old Order Amish provide unique opportunities to characterize contributions of rare variants to risk for psychiatric traits. The unique population structure resulting from population bottlenecks causes certain otherwise-rare variants to become enriched, including functional variants with large effects that are removed from the broader population due to their fitness costs. Here, we leveraged deep clinical phenotyping and exome sequencing data in a family-based Old Order Amish cohort (N = 4,327) to characterize rare variants associated with a lifetime history of depressive symptoms. The most significant association (FDR < 0.05) was with a missense variant in *ANK3*, encoding the axonal structural component ankyrin G, for which 13 carriers were diagnosed with mood disorders compared to 12 carriers with no history of mental illness. In addition, we identified a missense variant in *KCNH7*, encoding a voltage-gated potassium channel, for which 34 carriers were diagnosed with mood disorders compared to 45 carriers with no medical illness. Rare variants in both of these genes have previously been implicated in risk for neurodevelopmental disorders. Ongoing analyses of existing data from our cohort will enable detailed characterization of cognitive, behavioral, and brain imaging endophenotypes through which these variants may influence risk for mood disorders.

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Poster

PSTR336: Genomic and Transcriptomic Techniques (Human)

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR336.13/LL68

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

Title: CRISPR/Cas9 loss-of-function screen in a neuronal model of AP-4 deficiency identifies ATG9A trafficking modulators

Authors: *M. ZIEGLER[1], C. GÜNTER[1], J. ALECU[1], X. XUE[1], A. SAFFARI[1], A. K. DAVIES[4], M. SAHIN[2], D. EBRAHIMI-FAKHARI[3];
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Abstract: Biallelic loss-of-function variants in the adaptor protein complex 4 (AP-4) disrupt trafficking of transmembrane proteins at the trans-Golgi network, including the autophagy-related protein 9A (ATG9A), leading to childhood-onset hereditary spastic paraplegia (AP-4-HSP). AP-4-HSP is characterized by features of both a neurodevelopmental and degenerative neurological disease. To investigate the molecular mechanisms underlying AP-4-HSP and identify potential therapeutic targets, we conducted an arrayed CRISPR/Cas9 loss-of-function screen of 8,478 genes, targeting the ‘druggable genome’, in a human neuronal model of AP-4 deficiency. Through this phenotypic screen and subsequent experiments, key modulators of ATG9A trafficking were identified, and complementary pathway analyses provided insights into the regulatory landscape of ATG9A transport. Knockdown of ANPEP and NPM1enhanced ATG9A availability outside the trans-Golgi network, suggesting they regulate ATG9A localization. These findings deepen our understanding of ATG9A trafficking in the context of AP-4 deficiency and offer a framework for the development of targeted interventions for AP-4-HSP.

Disclosures: M. Ziegler: A. Employment/Salary (full or part-time):; University Hospital Zurich. 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.; Bayer Foundation, German Academic Exchange Service, German National Scholarship Foundation. **C. Günter:** 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.; German National Exchange Service, Biomedical Education Program, RWTH Aachen Research Ambassador Scholarship. **J. Alecu:** 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.; German National Academic Foundation, German National Exchange Service, Biomedical Education Program. **X. Xue:** None. **A. Saffari:** 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.; German Research Foundation, grant 448402208. **A.K. Davies:** 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.; European Union's Horizon 2020 research and innovation program, Marie Skłodowska-Curie grant agreement 896725. **M. Sahin:** A. Employment/Salary (full or part-time):; Rosamund Stone Zander chair. **D. Ebrahimi-Fakhari:** 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.; CureAP4 Foundation, Spastic Paraplegia Foundation, Manton Center for Orphan Disease Research, BCH Office of Faculty Development, BCH Translational Research Program, NINDS 1K08NS123552-01, 1U54NS148312.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.01/LL69

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Clinical Validation of Continuous Digital Measures Reveals Robust Rett Syndrome Phenotypes in the Clinically Relevant Sex

Authors: M. SIMON[1], A. E. CLIPPERTON-ALLEN[2], Z. BEAUDRY[3], L. SCHAEVITZ[1], K. FUHRMAN[4], J. ZYUZIN[5], N. DITTO[6], M. C. SAUL[7], ***N. BRATCHER-PETERSEN**[8], C. M. LUTZ[1];
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Abstract: Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder caused by pathogenic variants in *MECP2* and affects predominantly females. Despite substantial advances in gene-targeted therapeutics, translation remains constrained by the limited sensitivity and translational relevance of conventional preclinical endpoints, particularly in heterozygous female models that most closely reflect the clinical population. Behavioral assessments are often discrete and insufficiently sensitive to detect subtle or longitudinal disease manifestations limiting biological interpretation and therapeutic evaluation. Continuous digital measures of

behavior and physiology may improve detection of disease-associated phenotypes and provide objective, longitudinal assessments of disease progression, reducing the subjectivity of conventional evaluations. However, their utility in RTT requires validation with clinically relevant models and contexts of use. Here, we employed the adapted In Vivo V3 framework to clinically validate digital measures in a RTT mouse model by assessing biological relevance, phenotypic sensitivity, and translational interpretability across a hemizygous male and heterozygous female *Mecp2* model. Continuous digital measures identified RTT-associated deficits, including activity. Importantly, digital endpoints enabled robust phenotypic detection in heterozygous females, where conventional assessments often yield inconsistent or weak signals. Compared to conventional Bird severity scoring, continuous digital measures demonstrated greater sensitivity and dynamic range for detecting RTT-associated phenotypes, particularly in heterozygous females. Digital endpoints revealed persistent and progressive behavioral abnormalities that aligned with established RTT-associated deficits while providing greater sensitivity, temporal resolution, and scalability than conventional assessments, supporting their use as translational outcome measures. Continuous digital measures provide objective, longitudinal insight into RTT-associated behavioral and physiological changes, improving phenotypic characterization and therapeutic evaluation in the clinically relevant sex. By linking digital signals to biologically meaningful disease manifestations, this approach enables interpretable preclinical outcome measures that may accelerate the development and evaluation of emerging disease-modifying therapies.

Disclosures: M. Simon: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **A.E. Clipperton-Allen:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **Z. Beaudry:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **L. Schaevitz:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **K. Fuhrman:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **J. Zyuzin:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **N. Ditto:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **M.C. Saul:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **N. Bratcher-Petersen:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **C.M. Lutz:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.02/LL70

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: JST SPRING, Grant Number JPMJSP2119

Title: Targeting HNMT for Hypersomnia disorders; Mechanistic Insights Driving a New Therapeutic Modality

Authors: *T. MIMURA, F. NAGANUMA, T. YOSHIKAWA;
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Abstract: Hypersomnia disorders are marked by excessive daytime sleepiness (EDS) and unstable arousal, yet effective therapeutic options remain limited. Here, we propose that inhibition of histamine N-methyltransferase (HNMT) offers a broadly applicable strategy for treating hypersomnia disorders, including narcolepsy, idiopathic hypersomnia, and EDS associated with Parkinson's disease. Because HNMT is the primary enzyme responsible for degrading histamine in the brain, its inhibition provides a rational approach to elevating endogenous histamine levels and promoting wakefulness. In this study, we used *Hcrt*-knockout mice (a model of narcolepsy type1), *Sik3*-mutant mice (a model of idiopathic hypersomnia), and dopamine-neuron-degeneration mice (a model of Parkinson's disease) as experimental models of hypersomnia disorders. Pharmacological inhibition of HNMT markedly increased brain histamine concentrations and produced robust wake-promoting effects across those mouse models. These effects were accompanied by strong suppression of rapid eye movement (REM) sleep. To clarify the receptors involved, we performed pharmacological analyses. The wake-promoting effects of HNMT inhibition were abolished by histamine H1 receptor antagonism. In contrast, REM suppression was not altered by blockade of both H1 and H2 receptors, suggesting the involvement of other histamine receptor subtypes, particularly the H3 receptor. Histological analyses demonstrated the presence of H3R expression in brain regions essential for REM sleep regulation. Together, these findings support a potential role for H3 receptors in the regulation of REM sleep. In parallel with the detailed elucidation of the mechanism of action, we initiated an exploratory drug screening aimed at developing novel therapeutics for hypersomnia disorders through HNMT inhibition, as existing HNMT inhibitors have limited clinical applicability due to suboptimal pharmacokinetic properties. High-Throughput Screening identified eight candidates of core scaffold with favorable properties for further optimization. Ongoing derivatization and pharmacological evaluation aim to determine the most promising lead compound with optimal potency, selectivity, and pharmacokinetic characteristics. Together, these findings position HNMT inhibition as a promising approach to boosting brain histamine level and regulating sleep-wake states. Continued mechanistic and medicinal chemistry work could enable development of a broadly applicable therapy for hypersomnia.

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Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.03/LL71

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Pre-Treatment Directed EEG Network Dynamics Predict Response to rTMS in Treatment-Resistant Depression

Authors: *C. LEMAITRE[1], M. ARNS[3], A. CHARLES[1], S. V. SARMA[2];
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Abstract: Major depressive disorder (MDD) is one of the top three leading causes of disability worldwide, with a disproportionate burden carried by patients with treatment-resistant depression (TRD). TRD patients are eligible for neurostimulation interventions such as repetitive transcranial magnetic stimulation (rTMS), but only 30-50% respond. A marker for rTMS responsiveness would reduce remission rates, shorten time to effective care, and lower costs. We propose a novel network-based marker on pretreatment EEG to predict response to left dorsolateral prefrontal cortex (DLPFC) rTMS.

Using two-minute resting-state scalp EEG recordings from the TDBRAIN+ dataset (n = 54; 36 responders), we fit patient-specific Dynamic Network Models (DNMs) in sequential 84-ms windows. DNMs estimate directed interactions among EEG channels over time, producing a state-transition matrix (A) in which each element A_{ij} quantifies the influence of electrode j on the future activity of electrode i. Time-varying A_{ij} values were then analyzed to characterize the temporal evolution of network influence patterns associated with treatment response. Statistical significance was assessed using bootstrap resampling, permutation testing, and t-tests.

The DNM fit was strong, with mean reconstruction correlation to observed EEG at r^2 of 0.94 across patients. The top three statistically significant Aij connections were the median values of CPz→CP3, F3→T3, and C3→F4. F3, the stimulation target over the left DLPFC, had a positive influence effect on T3 in responders, whereas this connection is negative in nonresponders. C3→F4 also showed a sign reversal between groups, while CPz→CP3 was positive in both groups but larger in nonresponders. These findings suggest altered frontoparietal and frontotemporal directional dynamics in rTMS nonresponders, potentially reflecting differences in cognitive control and emotion-regulation network interactions.

The top three significant A_{ij} connections were then used to train a logistic model and classify responders versus nonresponders with 5-fold stratified cross-validation. The model achieved an accuracy of 0.855 ± 0.138, F1-score of 0.897 ± 0.090, and precision-recall curve AUC of 0.921 ± 0.049. Our work demonstrates a promising approach to uncover network differences within depression patients and to predict left rTMS response from first-visit resting-state EEG. Future work will include blinded out-of-sample validation and stratifying left and right rTMS responders for treatment stratification.

Disclosures: C. Lemaitre: None. **M. Arns:** None. **A. Charles:** None. **S.V. Sarma:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.04/LL72

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Trends in ongoing clinical psychedelic research critical for regulatory approval

Authors: *L. WITTENKELLER, G. A. GUDELSKY, T. WINHUSEN, D. AMATO;
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Abstract: Introduction: Serotonergic psychedelics have recently attracted renewed interest as potential therapeutics for psychiatric disorders, leading to a rapid increase in early-phase clinical trials across multiple conditions. Despite promising findings from early studies, regulatory approval remains challenged by methodological concerns, including functional unblinding and lack of consensus regarding placebo and comparator selection. Given the rapid expansion of psychedelic research, we sought to determine how ongoing trials address key critiques relevant to psychedelic approval and to identify emerging trends in trial design and therapeutic applications. Methods: Using a scoping systematic search strategy, we queried ClinicalTrials.gov for ongoing clinical trials involving psychedelic interventions. Indicated condition, trial characteristics, and experimental design features were characterized. Outcomes and assessment timepoints were extracted and summarized for the ten most frequently reported outcomes across trials. Results: We identified 178 ongoing clinical trials, most of which were early-phase, actively recruiting, based in the United States, and focused on depression. Psilocybin was the most frequently studied psychedelic, whereas no ongoing trials using mescaline were identified. Among 100 blinded trials, only seven reported blinding integrity as an outcome. More than 50 different placebos or comparators were used across studies, and 50 trials incorporated neuroimaging approaches. Conclusions: Psychedelic clinical research has expanded rapidly, yet critical methodological issues, including functional unblinding, placebo effects, trial continuity, and protocol standardization, remain largely unaddressed. These findings highlight the need for greater methodological consensus and more rigorous assessment of blinding, comparator selection, and longitudinal outcomes in ongoing psychedelic trials.

Disclosures: L. Wittenkeller: None. **G.A. Gudelsky:** None. **T. Winhusen:** None. **D. Amato:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.05/LL73

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH Grant R01MH133561
NIH Grant R01AG080790
NIH Grant R01AG076949

Title: Molecular landscapes of human hippocampus in major depressive disorders

Authors: M. PENG[1], ***J. JIANG**[1], L. POLIZZI[1], T. SHI[1], R. RAMKUMAR[1], V. ANOSIKE[1,2], G. GUASONI[1], A. M. WAMALWA[1], M. MARIANI[1], C. SISSOKO[1], A. TARTT[2], C. FULMORE[2], G. ROSOKLIJA[1], Y.-Y. HUANG[1], V. ARANGO[3], S. MCDONALD[2], N.

BITOLJANU[4], J. MANN[1], P. NGUYEN[1], A. J. DWORK[2], L. BROWN[1], R. HEN[1], H. GALFALVY[1], M. BOLDRINI[1];
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Abstract: Major depressive disorder (MDD) is associated with reduced hippocampal volume, altered connectivity, and impaired memory function, suggesting disrupted hippocampal plasticity. However, the cellular and molecular basis of hippocampal dysfunction in MDD remains incompletely understood. Here, we generated a comprehensive multi-omic atlas of the adult human hippocampus by integrating single-nucleus transcriptomic and chromatin accessibility profiling, spatial transcriptomics, proteomics, and histological validation from neurotypical controls and individuals with MDD. Across approximately 500,000 hippocampal nuclei, we identified major neuronal and non-neuronal populations and characterized cell-type-specific molecular alterations associated with MDD. Integrative analyses revealed widespread changes in transcriptional regulation, neuronal plasticity, cellular stress responses, and immune-associated signaling across hippocampal cell types. We also identified a putative adult neurogenic lineage composed of quiescent and activated neural stem cells (NSCs), intermediate neural progenitors, neuroblasts, and immature granule-cell populations. Rank-based signature scoring, trajectory inference, transcription factor network analyses, integration with fetal hippocampal datasets, and spatial transcriptomics supported the organization of these populations along a neurogenic progression. Comparison of MDD and control hippocampi revealed altered neurogenic dynamics characterized by accumulation of stem-like states, reduced neuroblast abundance, and delayed progression through the neurogenic lineage, consistent with halted neurogenesis rather than depletion of progenitor populations. Notably, NSCs and early neurogenic populations exhibited enrichment of interferon-response and stress-response pathways, linking disrupted neurogenic progression with inflammatory signaling programs. These alterations were accompanied by broader changes in neuronal plasticity and cellular stress pathways across multiple hippocampal cell populations. Together, these findings provide a high-resolution molecular framework of the human hippocampus in MDD and identify halted adult neurogenesis, accompanied by interferon-associated stem-cell dysregulation, as a prominent feature of hippocampal pathology in depression, highlighting potential therapeutic targets for future investigation.

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Poster

PSTR337: Neuropsychiatric Disorders

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.06/LL74

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NRF Grant 1711187922

Title: Comparative evaluation of various vagotomy techniques establishes left cervical vagotomy as the optimal preclinical mouse model for 'Wi-dam-jeok' (functional dyspepsia) research

Authors: *Y.-S. YANG;
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Abstract: Functional dyspepsia (FD), conceptualized in traditional Eastern medicine as 'Wi-dam-jeok', is characterized by chronic gastrointestinal (GI) dysmotility that is frequently accompanied by neuropsychiatric comorbidities such as anxiety and cognitive impairments. Investigating the pathophysiological mechanisms of FD requires a preclinical model that accurately reflects the gut-brain axis dysregulations without confounding structural abnormalities. This study aimed to establish an optimized vagotomy model in mice to simulate FD and comprehensively evaluate both GI motility and subsequent neurobehavioral alterations. We comparatively analyzed different surgical approaches, including abdominal truncal and cervical routes, as well as laterality (left, right, bilateral) in mice. Our evaluation revealed that the abdominal truncal approach induced severe postoperative adhesions, confounding GI motility assessments. Bilateral cervical vagotomy resulted in 100% mortality. However, compared to the sham-operated group, unilateral left cervical vagotomy successfully bypassed adhesion-related artifacts and induced the most significant GI motor dysfunction, specifically delayed gastric emptying and intestinal transit, mimicking the core GI symptoms of FD. Crucially, subsequent neurobehavioral assessments utilizing this optimized left cervical vagotomy mouse model revealed distinct neuropsychiatric alterations consistent with FD comorbidities. Compared to the sham controls, the mice exhibited significantly increased anxiety-like behaviors, as assessed by the open field test, and impaired memory function, evaluated using the Y-maze. Notably, no significant differences were observed in depression-like behaviors during the forced swimming test or basic motor functions on the rotarod, indicating specific cognitive and emotional deficits rather than generalized systemic impairment. These findings demonstrate that left cervical vagotomy in mice is a reliable and translational preclinical model for FD ('Wi-dam-jeok'). By successfully replicating the co-occurrence of severe gastrointestinal dysmotility and specific neuropsychiatric deficits without surgical artifacts, this model provides a critical platform for advancing gut-brain axis research and developing targeted therapeutics for functional gastrointestinal disorders.

Disclosures: Y. Yang: None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.07/LL75

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: Ministry of Food and Drug Safety (MFDS) of the Republic of Korea

Title: Developing an Integrated Brain Resource Framework for Translational Neuroscience in Korea Brain Bank

Authors: *H. SEOK[1], T. SON[3], K. KIM[3], J. KOO[4], P.-G. SUH[2];
[1]Korea Brain Res. Inst., Dae Gu, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of; [4]Emotion, Cognitive & Behavior Res. Group, [3]Korea Brain Res. Inst. (KBRI), Daegu, Korea, Republic of

Abstract: The Korea Brain Research Institute (KBRI) and its core facility, the Korea Brain Bank (KBB), are establishing a national framework that integrates human brain banking with digital and multi-omics resources to strengthen translational neuroscience in Korea. Operating under the Brain Research Promotion Act (BRPA) and supported by the Ministry of Science and ICT (MSIT), the KBB manages the designated Korean Brain Bank Network (KBBN), a national system that provides centrally coordinated nationwide coverage through eight network hospitals. The network is supported by the KBRI-developed Brain Resource Archive Management System (BRAMS) for integrated management of human brain resources. KBBN enhances interoperability, standardization, and data accessibility across the network. These efforts have led to measurable improvements in data completeness, resource utilization efficiency, and research connectivity. Since its establishment, KBBN has prioritized the collection of brain resources from patients with neurodegenerative disorders, enabling neuropathological assessment and digital dataset construction for integrated analysis. However, securing brain resources for psychiatric disorders remains limited due to sociocultural barriers to donation in Korea. To address this, KBB is expanding international collaboration to develop specialized psychiatric cohorts for joint multi-omics studies. Future strategies focus on increasing functional resource value through single-cell and spatial omics integration, linking postmortem-derived iPSC and organoid models, and establishing an AI-assisted federated data governance system that integrates imaging, genomic, and clinical data within a Brain Atlas Hub. Through the convergence of cellular innovation, digital governance, and global cooperation, KBB seeks to advance responsible and sustainable brain resource management in Korea.

Disclosures: H. Seok: None. **T. Son:** None. **K. Kim:** None. **J. Koo:** None. **P. Suh:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.08/LL76

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Epigenome-wide association study of Early Onset Psychosis in the Mexican population

Authors: *D. RUIZ[1], M. RAMOS MENDEZ[2], T. GONZÁLEZ-CASTRO[3], A. GENIS-MENDOZA[4], J. J. MARTÍNEZ-MAGAÑA[5], I. E. JUAREZ-ROJOP, Jr.[6];
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Abstract: Early-onset psychosis (EOP) is a mental disorder characterized by the onset of psychosis before the age of 18 years. Individuals with EOP tend to experience a worse prognosis and shorter life expectancy. The etiology remains unclear, although several reports have suggested that DNA methylation is an epigenetic mechanism that could serve as an interplay between environmental exposures and biological processes for the development of psychosis at an early stage. In this sense, authors have demonstrated DNA methylation associated with a first episode of psychosis and early-onset schizophrenia; however, there is little information about epigenetic biomarkers of early-onset psychosis in the Mexican population. The aim of the present study was to explore the associations between DNA methylation and early-onset psychosis in the Mexican population. We conducted a cross-sectional, descriptive study. Seventy-five subjects between the ages of 12 and 18 were included. Psychiatric assessment was evaluated with the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). The recruitment of the sample population took place at the Hospital Psiquiátrico Infantil Juan N Navarro. A peripheral blood sample was collected for DNA methylation analysis. Two comparison groups were selected: the EOP group (psychiatric patients with psychotic symptoms) and the non-EOP group (psychiatric patients without psychotic symptoms). EPIC v1 and EPIC v2 microarrays were harmonized for DNA methylation associations, and statistical analysis was performed using the available libraries in R (v 4.3.3). In our epigenome-wide association study, we identified two differentially methylated positions associated with EOP at a nominal level. These CPG sites (cg04243770 and cg10468580) were annotated on chromosome 17. The cg04243770 site was situated in the *KCNH4* gene, and the cg10468580 site was positioned in the *ANAPC11* gene. Both CpG sites were hypermethylated in the EOP group in comparison with the non-EOP group. Our findings suggest associations between DNA methylation and early-onset psychosis in the Mexican population, specifically in genes involved in the cell cycle, metaphase/anaphase regulation, and voltage-gated potassium channel expression. However, larger samples should be considered to replicate and provide insight into children's neurodevelopment within our population.

Disclosures: D. Ruiz: None. **M. Ramos Mendez:** None. **T. González-Castro:** None. **A. Genis-Mendoza:** None. **J.J. Martínez-Magaña:** None. **I.E. Juarez-Rojop:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.09/LL77

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: AION platform: A Rodent Ultrasonic Vocalization Signature Integrated with Head-Twitch Response and Synaptic Plasticity Biomarkers Reveals Differential Hallucinogenic and Non-Hallucinogenic Neuroplastogen Activity

Authors: *K. R. WALKER, A. MOREIRA DE SA, E. PASCHEN, C. J. MALTBY, E. LIUBISHKIN, J. PINTO, M. BIANCHI;
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Abstract: Background: Serotonergic psychedelics and 5-HT_2A agonists are attracting interest as neuroplastogens — compounds capable of rapidly remodelling synaptic architecture independent of their hallucinogenic properties. Dissociating hallucinogenic from non-hallucinogenic neuroplastogen activity remains a central translational challenge, as current assays rely on the head-twitch response (HTR), a single behavioural readout of 5-HT_2A engagement. Here, we present the Aion platform, integrating HTR, ultrasonic vocalisations (USVs), and synaptic plasticity biomarkers to generate a pharmacological signature capable of dissociating hallucinogenic from non-hallucinogenic profiles. **Methods**: Naive C57BL/6J male mice received DMT (1 mg/kg), psilocybin (1.5 or 3 mg/kg), the non-hallucinogenic 5-HT_2A agonist Ariadne (3 mg/kg), or vehicle (s.c.). HTR and USVs were recorded simultaneously over 20 minutes post-dose using a high-frame-rate infrared camera (90 fps) with a calibrated ultrasonic microphone and Sonotrack software. Naturalistic behaviours were assessed via splash test and nest building at 24-43 hours. Synaptosomes from prefrontal cortex (PFC) at 48 hours were quantified for SV2A, synaptophysin, PSD-95, and acetylated α-tubulin by western blot. **Results**: Psilocybin produced a robust HTR; DMT a modest but significant response; Ariadne no HTR above vehicle. All compounds reduced USV counts versus vehicle: hallucinogens by 53-57%; Ariadne by 42%. USV call type analysis identified compound-specific signatures: psychedelics enriched *U-shape* calls, consistent with heightened arousal, whereas Ariadne increased *Step Up* calls, associated with positive-arousal states. Neither compound class affected naturalistic behaviours at 24-48 hours. All compounds produced a convergent neuroplastogen signature in PFC: decreased acetylated α-tubulin and upregulated synaptic markers. **Conclusions**: By integrating HTR, USV call rate and type, and synaptic biomarkers, the Aion platform captures pharmacological resolution that HTR alone cannot provide. Divergent USV profiles represent a novel naturalistic behavioural discriminator, while the convergent synaptic signature confirms hallucinogenic activity is not required for neuroplastogen efficacy. The Aion platform is available as an integrated preclinical service for neuroplastogen characterisation.

Disclosures: K.R. Walker: None. **A. Moreira de Sa:** None. **E. Paschen:** None. **C.J. Maltby:** None. **E. Liubishkin:** None. **J. Pinto:** None. **M. Bianchi:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.10/LL78

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Molecular Biomarker Profiling of Hallucinogenic and Non-Hallucinogenic Neuroplastogens in Human iPSC-derived and Rodent Neuronal Models

Authors: *J. PINTO, J. KEATING, E. PASCHEN, C. J. MALTBY, M. BIANCHI; Ulysses Neurosci. Ltd., Dublin, Ireland

Abstract: Background: Major depressive disorder and other neuropsychiatric disorders remain significant unmet medical needs despite multiple therapeutic approaches. The emergence of ketamine and serotonergic psychedelics as rapid-acting therapeutics has highlighted neuroplasticity as a key mechanism underlying clinical efficacy. However, translational human-relevant platforms for screening neuroplastogen compounds remain limited. **Methods:** Primary rat cortical neurons and human iPSC-derived cortical neurons were exposed to ketamine and a panel of 5-HT_2A receptor agonists encompassing hallucinogenic and non-hallucinogenic compounds: psilocin, DMT, 5-MeO-DMT, and Ariadne. Neuronal network activity was assessed using high-density microelectrode array (HD-MEA; MaxWell) recordings. Morphological analyses used immunocytochemistry and Sholl analysis; synaptic plasticity was assessed through quantification of pre- and post-synaptic markers. Culture media BDNF was measured by ELISA and cytoskeletal remodelling through acetylated α-tubulin expression. Quantitative PCR (qPCR) characterised serotonergic receptor expression (HTR1A, HTR1B, HTR2A, HTR2C, SERT) across differentiation from week 0 to week 8. **Results:** Ketamine induced significant increases in dendritic arborisation, synaptic density, and BDNF release in primary cortical neurons; comparable responses were observed with serotonergic psychedelics. iPSC-derived cortical neurons demonstrated robust increases in dendritic complexity, synaptic marker expression, and extracellular BDNF, supporting their utility as a translational human screening platform. Neuroplastogen exposure induced coordinated structural and molecular remodelling, including increased SV2A and synaptophysin alongside altered acetylated α-tubulin dynamics, consistent with enhanced synaptic and cytoskeletal plasticity. qPCR confirmed serotonergic receptor expression across differentiation stages. HD-MEA studies are evaluating whether these adaptations translate into altered network activity. **Conclusions:** These findings establish complementary rodent and human neuronal platforms for neuroplastogen discovery and provide a translational framework for screening hallucinogenic and non-hallucinogenic compounds with therapeutic applications in neuropsychiatric disorders.

Disclosures: J. Pinto: None. **J. Keating:** None. **E. Paschen:** None. **C.J. Maltby:** None. **M. Bianchi:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.11/LL79

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Assessing treatment-associated brain network changes following a novel lithium treatment using 7T resting-state fMRI - results from a randomized phase 1/2A clinical trial

Authors: *S. DENG[1], M. AON[1], M. BROWN[1], S. FARINHA[1], M. SMITH[1], P. WEISER[1], T.-H. PHAM[1], D. REITBERG[2], E. DEL RIO[2], M. HENRY[3], K. ROAJPHLASTIEN[4], S. JACKMAN[4], K. DEVITTE-MCKEE[5], A. MCMANUS[5], J. GERBER[5], S. E. ARNOLD[5], H. TAFT[1], K. N. MAINA[1], S. A. NOLIN[1], J. E. CHEN[1], S. Y. HUANG[1], B. R. ROSEN[1], O. C. ANDRONESI[1];
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Abstract: Introduction. Lithium is the gold standard treatment for Bipolar Disorder, and often used in Major Depression Disorder, Schizophrenia or Alzheimer's Disease. However, its clinical utility is constrained by a narrow therapeutic window for inorganic Lithium salts which need careful monitoring to manage renal, thyroid, and other systemic toxicity risks. In this clinical trial we investigate treatment-related brain changes of AL001, a novel organic salt of Lithium co-crystalized with L-proline and salicylate designed for better brain delivery with less systemic exposure than inorganic salts.
Methods. To characterize the effects of AL001 on brain function, we performed longitudinal resting-state fMRI (rs-fMRI) at 7 Tesla in a randomized, phase 1/2A, multiple-dose, open-label, crossover clinical trial (NCT06921590). Six healthy participants completed baseline and two post-treatment imaging visits following two-week treatment with AL001 and the standard-of-care Lithium carbonate. Two-week washout was between treatments, and patients were balanced and randomized to treatment order. Rs-fMRI data were processed using fMRIPrep and XCP-D. Pairwise functional connectivity matrices were calculated from time series parcellated using the 4S156 atlas in XCP-D (Schaefer-100 cortical atlas with additional subcortical parcels). Analyses examined edge-level connectivity changes and network-level patterns, with exploratory network-level comparisons performed using Wilcoxon signed-rank tests.
Results. Our analysis suggests that post-treatment changes were not dominated by global connectivity shifts, but instead reflected distributed patterns of edge-level reorganization. Network-level summaries showed variable effects across participants, and no network-level effects survived correction for multiple comparisons in the current sample. Despite this, recurring involvement of sensory-motor/attention-related and subcortical-thalamic/cerebellar regions was observed among the more prominent changing edges, suggesting potential target networks for further evaluation as enrollment increases.
Conclusions. Preliminary results indicate that treatment-associated functional connectivity changes might be detectable at the edge level, supporting the feasibility of measuring brain effects of AL001 by rs-fMRI to guide its clinical translation. Our data suggests possible different modulation of brain activity by AL001 compared to Lithium carbonate.

Disclosures: S. Deng: None. **M. Aon:** None. **M. Brown:** None. **S. Farinha:** None. **M. Smith:** None. **P. Weiser:** None. **T. Pham:** None. **D. Reitberg:** F. Consulting Fees (e.g., advisory boards); Alzamend Neuro, Inc. **E. Del Rio:** F. Consulting Fees (e.g., advisory boards); Alzamend Neuro, Inc.. **M. Henry:** None. **K. Roajphlastien:** A. Employment/Salary (full or part-time):; Alzamend Neuro, Inc. **S. Jackman:** A. Employment/Salary (full or part-time):; Alzamend Neuro, Inc.. **K. Devitte-McKee:** None. **A. McManus:** None. **J. Gerber:** None. **S.E. Arnold:** None. **H. Taft:** None. **K.N. Maina:** None. **S.A. Nolin:** None. **J.E. Chen:** None. **S.Y. Huang:** None. **B.R. Rosen:** None. **O.C. Andronesi:** 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.; Alzamend Neuro, Inc..

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.12/LL80

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Support: NIH Grant U01MH130625
NIH Grant P50MH136297

Title: Substantia Nigra Pars Reticulata Deep Brain Stimulation Implicates Basal Ganglia-Thalamocortical Mechanisms in Auditory Verbal Hallucinations

Authors: *A. SHEN[1], A. SAWA[2,3,4,5,6], N. G. CASCELLA[2];
[2]Psychiatry and Behavioral Sci., [3]Neurosci., [4]Genet. Med., [5]Pharmacol. and Mol. Sci., [1]Johns Hopkins Sch. of Med., Baltimore, MD; [6]Mental Hlth., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD

Abstract: Auditory verbal hallucinations (AVH) are among the most disabling symptoms of schizophrenia and are traditionally linked to dysfunction within distributed language and auditory processing networks. Emerging evidence, however, suggests that basal ganglia-thalamocortical (BGTC) circuits may also contribute to hallucination generation. Deep brain stimulation (DBS) of the substantia nigra pars reticulata (SNr), a major basal ganglia output nucleus, has shown preliminary therapeutic potential in treatment-resistant schizophrenia (TRS), yet its physiological mechanisms remain poorly understood.
We performed simultaneous intraoperative electrocorticography (ECoG) and SNr DBS testing in a patient with TRS undergoing bilateral SNr DBS implantation. A temporary 63-channel ECoG grid was placed over left language processing cortex. During double-blinded DBS OFF and DBS ON periods, the patient continuously reported AVH onset and offset using a button press. Cortical activity was characterized by spectral power and theta-gamma phase-amplitude coupling (PAC), a measure of cross-frequency synchronization implicated in hierarchical information processing.

AVH episodes were associated with reduced gamma-band power within the angular and supramarginal gyri, accompanied by widespread elevations in theta-gamma PAC across language-related cortex. Significant cross-frequency coupling was confirmed using surrogate-based permutation testing. Spatial mapping identified focal PAC hotspots within inferior parietal and postcentral regions, suggesting localized cortical nodes involved in hallucination-related processing. Bayesian analyses further demonstrated robust AVH-associated PAC elevations at physiologically responsive cortical sites. Activation of SNr DBS attenuated these PAC abnormalities, shifting cortical synchronization patterns toward non-hallucinatory baseline states. Concurrently, patient-reported hallucination frequency decreased by 64%, and the temporal structure of AVH episodes was altered.
These findings provide real-time human electrophysiological evidence that modulation of a major basal ganglia output nucleus can rapidly influence cortical network dynamics associated with hallucinations. The results support a role for BGTC circuitry in AVH pathophysiology and identify theta-gamma synchronization as a candidate physiological marker of symptom expression and neuromodulation response. More broadly, this work demonstrates how simultaneous cortical recording and subcortical stimulation can be leveraged to investigate circuit-level mechanisms underlying psychiatric symptoms in humans.

Disclosures: A. Shen: None. **A. Sawa:** None. **N.G. Cascella:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

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Program #/Poster #: PSTR337.13/LL81

Topic: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

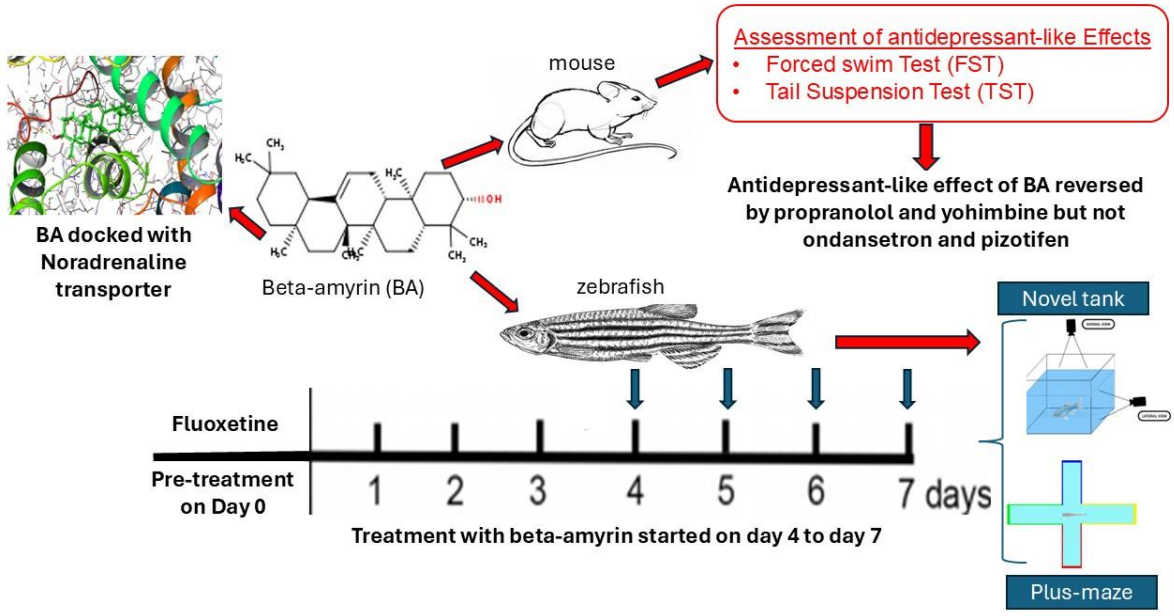
Support: DRIC-UCC Research Support Grant

Title: Antidepressant-Like Effects of β-Amyrin in Murine, Zebrafish, and In Silico Models: Involvement of Noradrenergic Neurotransmission Systems

Authors: *I. T. HENNEH[1], R. P. BINEY[2], D. AIDOO[3];
[1]Dept. of Pharmacotherapeutics and Pharm. practice, [2]Pharmacotherapeutics and Pharm. Practice, Univ. of Cape Coast, Cape Coast, Ghana; [3]Neuropsychopharm., Soochow Univ., Soochow, Ghana

Abstract: The study evaluated the antidepressant-like effects of β-amyrin (BA), a compound isolated from the African medicinal plant *Ziziphus abyssinica*, with reported neuroprotective and anti-inflammatory action. The antidepressant-like effect of BA (3, 10 and 30 mg/kg) was assessed using the forced swim test (FST) and tail suspension test (TST) in mice as well as the novel tank test (NTT) and plus-maze test (PMT) in adult zebrafish. The potential mechanism(s) of action of β-amyrin were examined in vivo using selective antagonism of serotonergic and adrenergic pathways, and molecular docking using the Maestro V13.5 of Schrödinger Suite

2023-1 and molecular dynamic simulation (MDS). The SwissAdme database and Protox were utilized to evaluate the pharmacokinetic and toxicity profile of BA. In both FST and TST, duration and frequency of immobility were significantly *(p*<0.05) reduced in mice pretreated with BA comparable to the effect of fluoxetine. In the NTT, zebrafish pretreated with reserpine, displayed depression-like behaviors which were reversed in zebrafish administered BA (3, 10, 30 and 100 µg/ml), via a significant (*p*<0.01) increase in duration spent in the upper half of the tank compared to control group fish. In the PMT, BA and fluoxetine-treated zebrafish exhibited similar behaviors by significantly increasing the frequency of entries into colored zones, compared to the zebrafish in the negative control group. Pretreatment with propranolol, a nonselective β-antagonist, and yohimbine (α2 antagonist) significantly reversed BA's antidepressant-like effects, while pretreatment with pizotifen and ondansetron did not significantly alter BA's effects in the FST and TST. In the in-silico assay, BA interacted fairly strongly with the norepinephrine transporter (NET) but weakly with the α-1B and α-2A receptors with docking scores of -6.818, -5.319, and -5.527 kcal/mol. BA did not bind to SERT, β-1 or β-2 receptors. MDS analysis shows BA binds to NET. Pharmacokinetic and toxicity evaluation indicated BA possesses generally favorable drug-likeness and safety profile.



Disclosures: I.T. Henneh: None. **R.P. Biney:** None. **D. Aidoo:** None.

Poster

PSTR337: Neuropsychiatric Disorders

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR337.14/LL82

Topic: I.04. Executive Functions

Support: NIH Grant R21MH118492
John and Patricia Cochran Scholars Fund
Passano Foundation Physician Scientist Award

Title: Abnormal Circulating miRNAs in Early-Stage Psychosis

Authors: *E. E. GERBER[1], D. MALLAH[2], F. C. NUCIFORA[1], A. SAWA[1], K. YANG[1], S. KANO[2];
[1]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Dept. of Psychiatry and Behavioral Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Psychosis is a state of impaired reality testing, often manifesting as hallucinations, delusions, and disorganized thinking. Psychosis occurs in a variety of conditions including disorders on the schizophrenia spectrum and is a frequent cause of disability. Currently, diagnosis and treatment are based on monitoring of clinical signs and symptoms, and there are no established quantifiable biological indices that correlate with clinical characteristics, diagnosis, underlying pathophysiology, condition severity, or treatment-responsiveness. Identifying biomarkers is a critical challenge in the field and would vastly improve prediction of diagnosis, prognosis, treatment-response, and patient care overall. Here we identify cell-free microRNAs (miRNAs) from blood that are promising biomarker candidates for longitudinal changes in clinical features in early-stage psychosis. We obtained cell-free miRNAs from peripheral blood in a cohort of early-stage psychosis patients and controls (60 patients; 57 controls) that were clinically characterized and followed over time. Profiles of cell-free plasma miRNAs differed significantly between patients and controls, and select miRNA levels correlated with disease severity and the rate of change in clinical features over time, including anhedonia, hallucinations, bizarre behavior, and total positive symptom score. Gene Set Enrichment Analysis revealed predicted targets of differentially expressed miRNAs were enriched for neuronal and synaptic function. Our findings demonstrate that select blood-derived cell-free miRNAs in early-stage psychosis correlate with initial and subsequent clinical changes, providing a framework for future discovery of biomarkers using liquid biopsy in psychosis.

Disclosures: E.E. Gerber: None. **D. Mallah:** None. **F.C. Nucifora:** None. **A. Sawa:** None. **K. Yang:** None. **S. Kano:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.01/LL83

Topic: J.06. Computation, Modeling, and Simulation

Support: Cleveland Clinic Neurological Institute Clinician Scientist Career Award

Title: Cross-Cohort Validation of a Structural MRI-Based Machine Learning Model for Motor Progression in Parkinson's Disease

Authors: *A. AMBILI VIJAYAKUMARI[1], O. HOGUE[2], R. POPOV[3], B. WALTER[1]; [1]Ctr. for Neurolog. Restoration, Cleveland Clin., Cleveland, OH; [2]Cleveland Clin., Cleveland Heights, OH; [3]Cleveland Clin., Beachwood, OH

Abstract: Predicting motor progression in early-stage Parkinson's disease (PD) remains clinically challenging due to marked inter-individual variability in disease trajectory. We previously developed a structural MRI-based machine learning model, derived from the Parkinson's Progression Markers Initiative (PPMI) cohort with standardized protocols, which shows promise for identifying patients at risk for faster motor progression. However, this model, termed PRIME-ML, has not yet been externally validated in heterogeneous cohorts. Here, we evaluate its generalizability across independent PD populations. We assessed PRIME-ML, a support vector machine classifier that predicts motor progression using multivariate gray matter volumetric distance (M_{GMV}) derived from 40 motor-relevant brain regions, along with age, sex, and baseline motor severity (MDS-UPDRS-III). The pre-trained model was applied without retraining to two independent external cohorts: the Cleveland Clinic Foundation (CCF) real-world clinical cohort (n=11), characterized by irregular follow-up and variable medication exposure, and the Parkinson's Disease Biomarkers Program (PDBP) research cohort (n=16), with scheduled assessments and predominantly medicated participants. Motor progression was defined using medication-adjusted annualized MDS-UPDRS-III slopes. Despite substantial differences in medication status, follow-up structure, and disease duration relative to the training dataset, PRIME-ML demonstrated encouraging discriminative performance. In the CCF cohort, the model achieved a balanced accuracy of 67.9% (sensitivity: 50%, specificity: 85.7%, AUC: 0.82), while in the PDBP cohort, performance was higher (balanced accuracy: 90.0%, sensitivity: 100%, specificity: 80%, AUC: 0.93). Notably, these results were obtained without model retraining or hyperparameter adjustment. These preliminary findings suggest that PRIME-ML retains discriminative ability across independent PD cohorts with heterogeneous clinical characteristics, supporting its generalizability beyond the original discovery dataset. However, further validation in larger, prospective cohorts with standardized assessments is needed to establish clinical utility and translational applicability in PD.

Disclosures: A. Ambili Vijayakumari: None. **O. Hogue:** None. **R. Popov:** None. **B. Walter:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.02/LL84

Topic: J.06. Computation, Modeling, and Simulation

Title: Edge Centric Dysfunction of Default Mode Network in Alzheimer's Disease Using Resting-State fMRI

Authors: *A. SARAN, A. BHARTI;
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Abstract: The connectivity of the default mode network (DMN) is disrupted in Alzheimer's disease (AD). Yet, graph-theoretical studies show topological differences in the nodal features aggregated from the regions of DMN. Here, we focus on functional synchrony by identifying the discriminating edges within the DMN, to understand specific cognitive processes disruption. We analyzed rs-fMRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) comprising 31 AD subjects and 40 cognitively normal (CN) subjects. After standard preprocessing using DPARSF, blood oxygen level-dependent (BOLD) time series were extracted from 26 DMN regions using AAL3 atlas. Pearson correlation coefficient (PCC) matrices were computed for all the subjects and these PCC are transformed using the Fisher Z-transformation. To capture the core properties of the network, i.e., segregation, integration and connectivity strength, we calculate degree, local clustering, betweenness centrality and average neighbor degree. We applied t-test on nodal features which showed no feature with significant group differences. We implemented the random forest (RF) classifier on nodal features, which resulted in an accuracy=0.513 and ROC-AUC=0.519. The performance was random and shows no feature is enough for discriminating AD and CN subjects. For edge-level analysis, all 325 edges of the DMN were used as features for RF classification. Edges were ranked by discriminability using Mann-Whitney U test (MWU). To prevent data leakage, ranking was performed on training data only. We trained an RF on Fisher Z-transformed values of ranked edges. We applied 5-fold cross validation (CV) with 10 repetitions and achieved the mean accuracy=0.64 and ROC-AUC=0.6880. Peak performance was achieved with hyperparameters, i.e., max_features = 5 (number of features for each split) and K=30 (top-K edges from MWU). We have tested the max_features value from 2 to 30 and top-k edges were considered from 10 to 100, at the interval of 5. The objective of the RF classifier was not just creating an effective classifier, but to find out the most discriminating edges. Feature importances from the RF were calculated using gini impurity. Eighteen edges were found to be consistently discriminating in more than 25 of the 50 CV-folds. The most distinct connections were focused within four integrated systems i.e., hippocampal-temporal memory pathways, PCC-based hubs in the DMN, cingulate regulatory circuits, and fronto-parietal association networks. Collectively, these systems provide the basis for episodic memory, semantic processing, attentional control, and cognitive integration, all of which are functionally impaired in AD.

Disclosures: A. Saran: None. **A. Bharti:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.03/LL85

Topic: J.06. Computation, Modeling, and Simulation

Title: Diagnostic Accuracy of Machine Learning EEG Classifiers for Schizophrenia: A Multilevel Meta-Analysis

Authors: U. TURAL[1], ***S. SHANNON**[1], D. V. IOSIFESCU[2];
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Abstract: Electroencephalography (EEG)-based machine learning (ML) approaches have increasingly been investigated as potential diagnostic tools for schizophrenia (SCH). However, studies often report heterogeneous findings, evaluating multiple classifiers within the same participant sample, potentially inflating effect estimates if treated as independent observations. This study synthesized the diagnostic accuracy of conventional ML-based EEG classifiers for SCH, irrespective of the EEG features involved in the predictor, while accounting for within-study dependence among classifier outputs. A database of EEG-based schizophrenia classification studies was systematically reviewed with analyses restricted to conventional ML approaches. Algorithms containing "SVM," "KNN," or "LDA" were grouped into support vector machine, k-nearest neighbors and linear discriminant analysis categories, respectively. Sensitivity and specificity were analyzed separately using multilevel random-effects meta-regression models in R (metafor package). Classifier estimates were nested within study as random effects using REML estimation, with algorithm family as a moderator. 8 studies comprising 274 schizophrenia participants and 255 healthy controls were included in the quantitative synthesis. 11 classifier outputs met inclusion criteria. Moderator analyses showed no significant differences between SVM, KNN and LDA classifiers for either sensitivity (QM[2] = 1.63, p = 0.44) or specificity (QM[2] = 2.14, p = 0.34). Residual heterogeneity was low and non-significant in both models (sensitivity: QE[8] = 4.29, p = 0.83; specificity: QE[8] = 5.06, p = 0.75). Pooled sensitivity estimates by algorithm (95% CI) were 91.4% (84.0-95.5) for SVM, 93.9% (82.0-98.1) for KNN and 87.8% (77.8-93.8) for LDA classifiers, while overall pooled specificity estimates were 92.7% (84.7-96.7), 86.7% (73.5-94.0) and 86.9% (75.5-93.4), respectively. Conventional EEG-based ML classifiers demonstrated high pooled sensitivity and specificity for schizophrenia classification across studies, highlighting the potential of this approach as a clinical tool. Importantly, our results represent the predictive ability of all potential EEG features. SVM classifiers showed numerically higher specificity, whereas KNN classifiers showed numerically higher sensitivity; however, algorithm-level differences were not statistically significant. These findings support EEG-based ML approaches as potential adjunctive tools for schizophrenia classification, although future studies are needed to better characterize the electrophysiological features driving model performance.

Disclosures: U. Tural: None. **S. Shannon:** None. **D.V. Iosifescu:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.04/LL86

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant P50HD105354
Marsh Refractory Epilepsy Research Program

Title: Standardized intracranial EEG profiling for comparing network connectivity across mouse models of neurodevelopmental disorders

Authors: *J. DONG[1], Y. OH[2], Y. SINGH[1,3], Y. WEI[1,3], A. MADHIRA[1,3], E. MARSH[1,4]; [1]Neurol., [2]Pediatrics, Children's Hosp. of Philadelphia, Philadelphia, PA; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Neurol., Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Intro: Electroencephalography (EEG) is a cornerstone technique for validating and building mechanistic understanding of mouse models of neurodevelopmental disorders (NDDs). Comparing EEG across NDD models and experimental setups poses inherent challenges, including differing strategies for feature computation, inconsistent electrode positioning, and throughput limits when analyzing large datasets. A standardized approach to cross-model EEG comparison will yield insight on whether disorders with similar presentations or mechanisms produce similar changes in EEG markers. To address this, we developed NeuRodent, an open-source Python package that standardizes window-based EEG/LFP feature extraction and population spike detection across recording formats and datasets, which makes cross-model comparisons feasible.
Methods: Using existing EEG recordings from the lab, starting with two mouse models with identical intracranial electrode positions, we compared NeuRodent output between models and controls. The two models were a Sox5 homozygous knockout (model of Lamb-Shaffer syndrome) and a tamoxifen-induced $Arx^{f/y}$;Rosa26-$CreER^{T2}$ model (ARXRosa, modelling ARX related disorders) with each compared against its respective wild-type cohort. For every model we quantified window-based features per channel (RMS amplitude, raw band power, relative band power, 1/f slope, and population spiking frequency) and cross-regional connectivity (Pearson correlation, coherence magnitude, and imaginary coherence). Features were compared across genotype, sex (where applicable), and time of day, using generalized linear mixed models.
Results: Across both models, no genotype or treatment effects were significant across features (ARXRosa $p \geq 0.08$; Sox5 $p \geq 0.07$). Beta and/or gamma band power varied with time of day in both models ($p \leq 0.038$), and gamma coherence showed a sex difference in the Sox5 model (males have lower coherence, $p = 0.046$).
Conclusion: Standardized profiling detected circadian and sex-related EEG markers while finding spectral and basic connectivity features preserved across genotypes at current sample sizes, indicating no genotype-specific changes in these two models. Ongoing analyses extend this cross-model comparison to additional mouse strains ($Arx^{f/y}$;PVCre, IQSEC2, CDKL5, STXBP1, AP3B2, and MSUD), connectivity measures (Granger causality, cross-regional phase amplitude coupling, phase locking value), and spectral parameterization.

Disclosures: J. Dong: None. **Y. Oh:** None. **Y. Singh:** None. **Y. Wei:** None. **A. Madhira:** None. **E. Marsh:** 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.; Ionis Pharma, Neurogene

Inc, Taysha Inc, Harmony Biosciences, SK Life Science, Curaleaf Inc. F. Consulting Fees (e.g., advisory boards); Ionis Pharma, Neurogene Inc, Taysha Inc, Acadia Inc.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.05/LL87

Topic: J.06. Computation, Modeling, and Simulation

Support: Once Upon a Time Foundation

Title: Nonlinear Models Do Not Outperform Linear Models in Forecasting Human Deep-Brain Micro-LFP Dynamics Across Rest and Movement

Authors: *M. ASADI[1], S. JAVADZADEH NO[2], A. SEYYED MOUSAVI[3], E. NOZARI[4], T. D. SANGER[5];
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Abstract: Neural activity is often expected to exhibit complex dynamics that may require nonlinear models for accurate prediction, particularly during voluntary movement. Although nonlinear architectures are widely used to model neural time series, recent studies suggest that linear models can also provide strong short-term predictions in resting-state macroscopic neural recordings, including fMRI and macro-LFP. Whether this principle extends to human deep-brain micro-local field potential (micro-LFP) recordings and whether it holds during voluntary movement remains unclear. Here, we tested whether nonlinear models improve forecasting of deep-brain neural activity during rest and movement.
In this work, we analyzed micro-LFP recordings from deep-brain nuclei acquired during deep brain stimulation (DBS) procedures in pediatric patients diagnosed with dystonia. Neural activity was segmented into resting and movement-related periods, and models were trained to forecast future neural activity from recent neural history. We compared scalar and multivariate linear autoregressive (AR) models with a set of nonlinear recurrent and residual neural-network models. Model performance was evaluated using cross-validated predictive power for one-step-ahead and multi-step-ahead forecasting, together with residual whiteness to quantify the temporal structure left unexplained by each model.
Across both rest and voluntary movement conditions, nonlinear recurrent neural-network models did not outperform linear AR models. This pattern persisted as the prediction horizon increased. Movement-related activity did not reveal a clear benefit of nonlinear modeling, despite the expectation that behavioral engagement may introduce richer dynamics. Residual nonlinear models similarly failed to improve prediction accuracy beyond linear baselines, reinforcing the latter’s apparent optimality for describing micro-LFP dynamics.
These findings suggest that the predictable component of human deep-brain micro-LFP activity, across behavioral states and increasing prediction horizons, can be largely captured by linear

temporal dependencies. More broadly, these results support interpretable linear system-identification models as practical tools for characterizing—and potentially controlling—deep-brain dynamics.

Disclosures: M. Asadi: None. **S. Javadzadeh No:** None. **A. Seyyed Mousavi:** None. **E. Nozari:** None. **T.D. Sanger:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.06/LL88

Topic: J.06. Computation, Modeling, and Simulation

Support: Raynor Cerebellum Project

Title: Detecting Network-Level Spike Bursting in Human Intracranial Recordings Through Hierarchical Rank Surprise Algorithm

Authors: *T.-L. CHANG[1], A. SEYYED MOUSAVI[1], S. JAVADZADEH NO[1], T. D. SANGER[2];
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Abstract: Transient high-frequency clustering of action potentials, or bursting, is an ubiquitous feature of neuronal activity across species and can be a hallmark of abnormal brain states. It is increasingly understood as a coordinated event spanning anatomically distinct regions beyond isolated units. Existing network burst detectors were developed on multi-electrode arrays lacking anatomical information and treat all channels as one undifferentiated pool, so none distinguishes synchrony within a single region from coordination across regions. Most also require fixed thresholds or assume a specific interspike interval distribution. We developed a hierarchical extension of the Rank Surprise method, a nonparametric burst detector that depends only on interval rank ordering. Detection proceeds across three scales: unit (bursts within single spike units), region (coordinated bursting among units within an anatomical region), and network (coordination across regions). To detect cross-channel synchrony, we generate surrogate spike-trains from each recording channel that preserve each channel's own burst structure while removing coordinated timing, serving as a null against which region and network onsets are tested. This isolates genuine coordination and prevents any single hyperactive unit or region from dominating at higher scales. The formulation also corrects the two limitations noted by the original Rank Surprise authors: firing-rate drift across the recording and the burst-pause regime, where long quiescent gaps leave within-burst intervals statistically unremarkable. In a confirmatory validation, we evaluated the method on synthetic spike trains with embedded ground-truth bursts, intracranial sEEG recordings from pediatric dystonia patients, and mouse recordings. Across all datasets, detections separated into single-channel, regional, and network bursts, tracking the true anatomical organization of the recording. As a control, stripping region

and channel labels to pool all channels into a single set changed which bursts were detected, confirming that network, regional, and single-unit bursts are distinct events rather than the same activity detected at different scales. The method also correctly flagged bursts in the burst-pause and nonstationary firing-rate regimes where the original Rank Surprise method fails. Because detection requires no fixed thresholds and no assumptions about spiking characteristics, the method generalizes across recording conditions and modalities, distinguishing bursting confined to one region from bursting that spans regions. Code is open source.

Disclosures: T. Chang: None. **A. Seyyed Mousavi:** None. **S. Javadzadeh No:** None. **T.D. Sanger:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.07/LL89

Topic: J.06. Computation, Modeling, and Simulation

Title: Detecting Drug-Induced EEG Alterations with Deep Learning: A Methodological Proof-of-Concept Study in Rats treated with MK-801

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[2]Pharmacol., [1]BIOTRIAL PHARMACOLOGY, RENNES, France; [3]BIOTRIAL NEUROSCIENCE, RENNES CEDEX, France

Abstract: Deep learning methods for electroencephalography (EEG) analysis are expanding rapidly, but architectures developed for human multichannel recordings are not necessarily well suited to animal EEG, as they typically involve far less channels. In the present study we have investigated whether deep learning could detect EEG alterations induced by the glutamatergic NMDA receptor (NMDAr) antagonist MK-801 (dizocilpine) in rats. EEG data was acquired from male Sprague-Dawley rats instrumented with telemetry implants, in a latin square crossover design treatment allocation scheme (including vehicle and multiple MK-801 dose levels). Spontaneous EEG recordings and event-related potentials (ERPs) from frontal and temporal electrodes were segmented into 0.5-s epochs and processed using a minimal preprocessing pipeline. Several candidates of deep-learning architectures were evaluated on classification tasks. Among those, EEG Conformer provided the best balance between performance and robustness. On the recording-level test set, the final model reached an F-score close to 0.90. Under a complementary leave-one-subject-out cross-validation, the mean F1-weighted score was 0.646 ± 0.034 (n = 5 folds), indicating that a genuine MK-801-related EEG signature transfers to unseen animals. In recordings from MK-801-treated rats, abnormal-class outputs increased with dose, from 0.17 at 0.025 mg/kg to 0.62 at 0.2 mg/kg. Auditory stimulation conditions increased abnormal classification relative to non-stimulated epochs, indicating improved sensitivity under stimulation conditions. These findings support the feasibility of using deep learning to detect compound-related EEG alterations in low-channel rat telemetry recordings with limited

preprocessing. These results also suggest that the approach may provide a useful complement to conventional analytical pipelines (i.e., standard spontaneous EEG and ERPs approaches) and support more automated and standardized preclinical EEG workflows for both safety and efficacy pharmacology studies.

Disclosures: F. Adraoui: A. Employment/Salary (full or part-time):; Biotrial. **G. Viardot:** A. Employment/Salary (full or part-time):; Biotrial. **K. Carvalho:** A. Employment/Salary (full or part-time):; Biotrial.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.08/LL90

Topic: J.06. Computation, Modeling, and Simulation

Support: NATO Science for Peace and Security Programme (BIONIC, #G8447)

Title: A Comparative Evaluation of State-of-the-Art Algorithms for Up and Down States Detection in Intracortical In Vivo Recordings

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Abstract: Slow Oscillations (SOs) are one of the most fundamental kinds of neural network activity. They are constituted by the bistable succession of high synaptic excitability and hyperpolarization states (UP and DOWN states, respectively). SOs modulate several processes including neural synchronization and memory consolidation. For these reasons, they are a promising target for neurostimulation protocols aimed at enhancing physiological functions or rectifying pathological brain activity. However, the development of such strategies has been hindered by the lack of comprehensive benchmarking of algorithms for their detection from electrophysiological recording. This work presents a comparative evaluation of four state-of-the-art algorithms (Saleem et al., 2010; Zucca et al., 2017; Kim et al., 2019; Dasilva et al., 2020) for the detection of cortical SO states. These methods were tested using two datasets (Neto et al., 2016; Zucca et al., 2017), both composed of simultaneous extracellular and juxtacellular rodent recordings. The membrane potential from the latter was used as the groundtruth for scoring algorithms performance on the former. Performance was summarized using standard classification metrics (i.e., accuracy, sensitivity, specificity, F1-score, etc.) and the Coincidence Index (Mukovski et al., 2007).The statistical analysis of the results was performed using Generalized Linear Mixed Models (GLMM) to account for the hierarchical structure of the dataset. It revealed that approaches based on instantaneous phase (Pasquale and Saleem) outperform other methods across all metrics ($p < 0.001$). This holds for both UP and DOWN states detection, indeed they achieved high levels of sensitivity and specificity for both states.

The Pasquale algorithm, which integrates SO phase with high-frequency beta and gamma band power, established a gold standard for SO detection by maintaining high sensitivity and specificity. Conversely, Kim algorithms, exploiting an amplitude-based thresholding, showed balanced performance over UP and DOWN states but moderate discrimination with high variability across recordings. The Dasilva method, based on log-transformed Multi-Unit Activity (MUA) proxies, exhibited bias toward DOWN states and unbalanced performance over datasets, suggesting performance susceptibility due to different signal properties without substantial re-tuning. Collectively, the results establish that low frequency activity phase is the most informative and dataset-invariant feature for identifying SO states. This research will provide foundations for the development of state-dependent closed-loop neuroprosthetics.

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Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

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Topic: J.06. Computation, Modeling, and Simulation

Support: NIH 1U24MH130988-01
1UM1TR004906-01
1R01AG066749-01

Title: ADInteractome: Discovering Alzheimer's Disease-Associated Gene Interactions from Single Nucleus RNA-seq Data through Neural Interaction States

Authors: *N. S. MAURYA[1], Y. WU[2], Y. YANG[4], W. CHEN[1], Z. LIU[3], Z. XU[5], W. ZHENG[1]; [1]MSBMI, Univ. of Texas health Sci. Ctr. Houston, Houston, TX; [2]Inst. for Hlth. Informatics, Univ. of Minnesota Twin Cities, Saint Paul, MN; [3]Dept. of Computer Sci., Univ. of Minnesota Twin Cities, Minneapolis, MN; [4]MD Anderson Cancer Ctr., Houston, TX; [5]Dept. of Computer Sci., Stevens Inst. of Technol., Santa Clara, CA

Abstract: Alzheimer's disease (AD) is a prevalent neurodegenerative disorder whose molecular mechanism remains poorly understood. Recent advances in single-nucleus RNA sequencing (snRNA-seq) have revealed the cellular heterogeneity of AD brains, yet most methods for inferring gene interactions rely on predefined biological priors that constrain discovery of novel, context-specific relationships. Development of an interpretable and scalable AI framework ADInteractome that discovers AD-associated gene-gene interactions directly from the internal states of neural networks trained on snRNA-seq data, without prior interaction labels. The concept is if a network can classify whether a cell is AD-associated from its expression, its internal representations must encode informative gene-interaction patterns. The neural interaction states were formalized and extracted from a single-cell Transformer (CelluFormer,

attention-derived) and an MLP (weight-derived), then aggregated across layers and cells, normalizing and ranking gene-gene pairs and building cell-type-specific interaction graphs. These methods were applied to the SEA-AD dataset (42 high-AD, 9 non-AD donors; 18 neuronal cell types), and findings were validated by enrichment analysis, independent databases, and virtual perturbation.Classifiers achieved high predictive accuracy, with 13 of 18 cell types yielding a macro F1 score above 0.9. Ranked interactions exhibited significantly stronger enrichment for established AD-associated relationships (BioGRID, DisGeNET) than co-expression baselines (Pearson correlation, CS-CORE, and a Diamond-inspired method). Across four of five excitatory neuron subtypes (Chandelier, L5/6 NP, L6 CT, and L5 ET), DLG2 - a postsynaptic scaffold protein emerged as a central hub, interacting with glutamatergic receptors (GRIA2/3, GRIN1), calcium/calmodulin-dependent kinases (CAMK2A/B/G), and synaptic partners (SNAP25, CACNG3), positioning it as a molecular convergence point whose disruption may drive early synaptic failure. Virtual knock-out/knock-in perturbation supported the DLG2 hypothesis: CelluFormer-selected gene pairs recovered AD-classification accuracy whereas randomly selected pairs did not (Mann-Whitney U test; L5 ET, $p = 0.0028$; L6 CT, $p = 0.0121$). Cross-referencing against Open Targets (IntAct, Reactome, STRING) confirmed core interactions, including GRIN1–DLG2 and GRIA2/3–DLG2. ADInteractome offers a scalable, interpretable, and data-driven framework for mapping disease-relevant gene-gene interactions in single-cell transcriptomic data.

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Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

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Program #/Poster #: PSTR338.10/LL92

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R00NS123113

Title: Channel Capacity as a novel time-resolved effective connectivity measure for intrinsic neural noise characterization

Authors: *J. JIAN, N. XU;
Fischell Dept. of Bioengineering, Univ. of Maryland, College Park, MD

Abstract: Effective connectivity (EC) characterizes directed causal influences among brain regions, but there remains a need for EC measures that capture both causal directionality and temporal variability while minimizing model assumptions. To address this need, we propose sliding-window channel capacity as a novel EC measure. We model the directed interaction from one region of interest (ROI) to another as a communication channel with a finite impulse response (FIR) filter and additive white noise. Channel coefficients are estimated directly from

neural recordings using linear regression, while the regression residuals are treated as noise samples. We quantify the EC using channel capacity, an information-theoretic measure representing the maximum rate at which information can be transmitted through a channel under a given signal power constraint. Unlike conventional approaches, this framework characterizes noise directly from the residual distributions without assuming Gaussianity. A sliding-window implementation enables the estimation of time-varying channel capacity and, consequently, dynamic effective connectivity. We validated the proposed measure using multiple neural recording modalities. First, directional asymmetry was evaluated using bilateral local field potential (LFP) recordings. The observed asymmetry in channel capacity was significantly smaller than scan-to-scan variability, indicating the absence of spurious directional connectivity. Second, task fMRI data from the Human Connectome Project were used to assess sensitivity to task-dependent changes in connectivity among task-related ROIs. The results showed higher sensitivity than the conventional benchmark Granger causality. Finally, we compared channel capacity estimates computed with and without the Gaussian noise assumption using EEG and LFP recordings. The results demonstrated measurable differences between the two approaches, highlighting the importance of accurately characterizing neural noise distributions. These findings establish sliding-window channel capacity as a principled EC measure that captures both causal directionality and temporal variability without requiring Gaussian noise assumptions. This framework provides a sensitive and theoretically grounded approach for investigating dynamic brain connectivity across neuroimaging modalities.

Disclosures: J. Jian: None. **N. Xu:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.11/LL93

Topic: J.06. Computation, Modeling, and Simulation

Support: Brain Science and Brain-like Intelligence Technology—National Science and Technology Major Project (2022ZD0204600)

Title: Beyond Point Estimates: Probabilistic Neural Response Prediction via Activity-Aware Hybrid Binning

Authors: *W. WANG[1], T. QIAN[2], W. LI[1];
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Abstract: Neural responses to sensory stimuli exhibit substantial trial-to-trial variability, which reflects not merely measurement noise but potentially intrinsic mechanisms of neural computation, and carries fundamental importance for understanding sensory coding. However, mainstream deep neural encoding models operate exclusively under a deterministic point-

estimation paradigm, approximating only the conditional mean while discarding the rich information embedded in response variability. Extending neural response prediction from scalar regression to full conditional distribution estimation is a necessary step toward characterizing the uncertainty structure of neural coding. This work reformulates neural response prediction as a K-bin probability distribution task: the model directly outputs a probability vector over possible response values. On deconvolved two-photon calcium imaging traces from the Sensorium 2023 dataset, to address the clear separation between resting and active states in the response distribution, a hybrid binning strategy is designed: the first bin is semantically anchored at the resting-state boundary, while the active-state range is partitioned into nearly equal-proportion intervals via quantile boundaries derived from the empirical response distribution, which directly counteracts the extreme class imbalance that plagues conventional equal-width discretization. Under the classic Core-Readout architecture, the regression head of the conventional Gaussian readout is replaced with a classification head and trained end-to-end via cross-entropy loss. Statistical analysis confirms the bimodal structure of the response distribution, with sub-threshold resting activity accounting for ~81% of all frames, consistent with the design assumption of the hybrid binning strategy. Across bin counts from 2 to 32, the hybrid 8-bin configuration achieves a single-trial correlation of 0.238 between the expected value of the predicted distribution and the observed response, surpassing the Gaussian baseline (0.234). Reliability Diagram analysis on held-out repeated-stimulus trials across 10 sessions confirms that predicted bin probabilities are consistent with empirical response frequencies, demonstrating that the model captures stimulus-conditional distributions rather than merely memorizing marginal bin frequencies. This approach provides a viable framework for uncertainty quantification and stochastic sampling, with potential applications in visual neural encoding and synthetic data generation.

Disclosures: W. Wang: None. **T. Qian:** None. **W. Li:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.12/LL94

Topic: J.06. Computation, Modeling, and Simulation

Support: Army Research Office W911NF-22-1-0223
NSF DMS Grant 2052499

Title: Spatially-Informed Biologically Interpretable Machine Learning Approaches for Analyzing Neural Data

Authors: *M. C. CRUZ, D. B. FORGER;
Univ. of Michigan, Ann Arbor, MI

Abstract: Modified Hodgkin-Huxley neuron models have previously been used in biological neural networks (BNNs) to classify neural data, including electroencephalography (EEG) recordings. This study extends the use of such BNNs by applying backpropagation to networks of biophysically accurate model neurons to generate EEG-like signals, predict brain states, and analyze EEG neurophysiology using parameters derived from the trained networks. In particular, we trained BNNs to exhibit different frequencies observed in EEG recordings and found that the variability of synaptic weights and applied currents increased with the target frequency range. Although these BNNs provide biological interpretability, they treat each EEG channel independently without considering the spatial relationships present in real EEG measurements. To address this limitation, we extend the architecture to incorporate spatial information, including physical distances and functional connectivity across regions, as additional hyperparameters. With these metrics, the adapted BNNs can infer activity associated with deeper brain regions, while neurons in hidden layers remain biologically interpretable and visualizable. Classification accuracy on single-subject data remains comparable to that of previous models when classifying varying consciousness levels, while cross-subject classification improves significantly. Furthermore, incorporating physical distances between electrodes further enhances accuracy.
Together, these findings highlight the importance of spatial relationships in biological neural networks. Analyses of the learning mechanisms of the BNNs reveal spatiotemporal patterns across the network, including traveling waves, providing new insight into the dynamics of brain activity and improving interpretability through spatially-informed learning.

Disclosures: M.C. Cruz: None. **D.B. Forger:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

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Program #/Poster #: PSTR338.13/LL95

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF 2342866
NIH 1R21AG101586

Title: A Sparse Markov Likelihood Framework for Inferring Effective Connectivity Motifs from Neural Spike Sequences

Authors: *M. YOUSUF[1], L. PAGNIER[1], M. CHERTKOV[1], J.-M. FELLOUS[2];
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Abstract: Understanding how measured population spike trains arise from underlying effective connectivity is a central challenge in data analyses, modeling memory, navigation, and decision-making processes. Hippocampal replay involves the internally generated reactivation of neural activity patterns during sleep and rest and is thought to contribute to memory consolidation. The

phenomenon of replay is ideal in that it does not strongly depend on external stimuli, making it a useful framework for studying the changes in directed, functional structure within neural populations. We model replay sequences as a first-order Markov process and introduce a computationally efficient One-Step Transition Maximum Likelihood Estimation (OST-MLE) framework for estimating directed effective connectivity from simultaneously recorded spike trains. OST-MLE models each neuron's future firing probability as a function of the current network state and infers sparse directed influence graphs by maximizing the conditional likelihood of observed state transitions. Replay sequences were generated from biophysically grounded hippocampus CA3 place-cell network simulations incorporating conductance-based neuronal dynamics, realistic AMPA and NMDA synaptic transmission, and in vivo-like stochastic synaptic background activity. Controlled connectivity motifs provided known ground-truth directed interactions for validation. OST-MLE robustly recovers ground-truth directed connectivity from replay sequences and reconstructs replay-associated network motifs embedded within the simulated CA3 network, even under sparse firing regimes. The inferred motifs are represented as sparse directed graphs whose edge weights quantify conditional influences among neurons. We extend OST-MLE to partially observed neural populations, enabling inference when only a subset of replay-participating neurons is recorded. The proposed framework offers a general, scalable approach for estimating effective connectivity from population spike data in stochastic neural systems, with potential applicability to probabilistic neural modeling and computational analyses of memory-related network dynamics.

Disclosures: M. Yousuf: None. **L. Pagnier:** None. **M. Chertkov:** None. **J. Fellous:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.14/LL96

Topic: J.06. Computation, Modeling, and Simulation

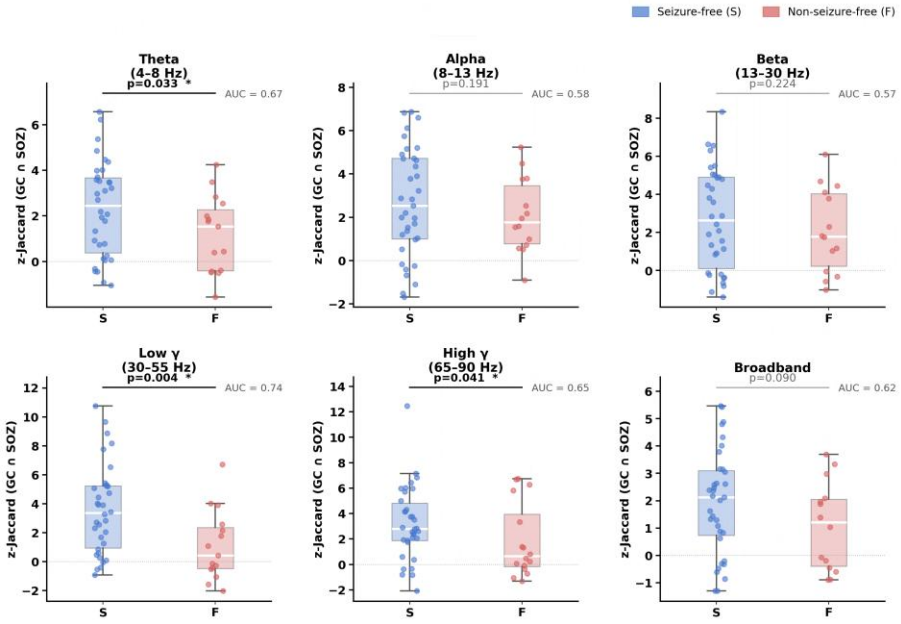
Support: Flagship of Advanced Mathematics for Sensing, Imaging and Modelling (FAME) funded by the Research Council of Finland.

Title: A dynamic network biomarker approach for localization of seizure onset zone from intracranial EEG

Authors: *N. PUTHANMADAM SUBRAMANIYAM[1], J. A. HYTTINEN[2];
[1]Fac. of Med. and Hlth. Technol., [2]Tampere Univ., Tampere, Finland

Abstract: Surgical resection offers the most effective treatment in patients with drug-resistant epilepsy, yet precise and reliable biomarkers for localizing the seizure onset zone (SOZ) remain limited. We hypothesized that seizure onset is preceded by the emergence of a transition core, a subset of intracranial EEG (iEEG) electrodes, whose collective dynamics predict the critical transition to seizures. To identify this transition core, we developed MI-GDNB, a dynamic

network biomarker (DNB) framework that combines normalized mutual information (MI) and giant component (GC) analysis from percolation theory. We applied our approach to iEEG signals from 54 drug-resistant epilepsy patients across 200 preictal recordings from the open-access HUP iEEG Epilepsy Dataset (38 seizure-free (S), 16 non-seizure-free (F) following surgery). Spatial concordance between preictal GC and clinically defined SOZ was quantified using z-Jaccard similarity and averaged across recordings for each patient. Concordance was compared between outcome groups using the Mann-Whitney U test and the area under the ROC curve (AUC). GC-SOZ concordance was significantly higher in seizure-free patients in low gamma ($p = 0.004$, AUC = 0.75), theta ($p = 0.033$, AUC = 0.67), and high gamma ($p = 0.041$, AUC = 0.65). These findings suggest that the preictal giant connected component identifies the hypothesized **transition core** underlying seizure generation and that successful surgical outcomes are associated with greater overlap between this network and the clinically defined SOZ. MI-GDNB is computationally efficient, applicable to standard clinical iEEG, and may offer a general strategy for identifying transition cores that precede pathological state changes across neurological disorders.



GC-SOZ z-Jaccard. Boxes show median and IQR. Dots show individual patients (Seizure-free (S) inblue and Non-seizure-free (F) in red). Significant bands marked with * (Mann-Whitney $p <$ 0.05, one-tailed S > F).

Disclosures: N. Puthanmadam Subramaniyam: None. **J.A. Hyttinen:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.15/Web Only

Topic: J.06. Computation, Modeling, and Simulation

Title: Uncertainty-Aware Deep Learning for Reliable Neurodegenerative Disease Diagnosis from Brain MRI: Calibration, Uncertainty Quantification, and Clinically Interpretable Confidence Reporting

Authors: *T. MORGÜL;
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Abstract: The early-stage diagnosis of neurodegenerative diseases (particularly Alzheimer's) using Magnetic Resonance Imaging (MRI) is of critical importance in clinical neuroimaging. However, standard deterministic deep learning models frequently produce overconfident clinical misclassifications when encountering out-of-distribution (OOD) or atypical neuroanatomical data. This study investigates the efficacy of uncertainty-aware neuromodels that quantify both aleatoric and epistemic uncertainties in structural MRI to ensure diagnostic reliability. Utilizing MRI and diffusion MRI datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts, the neuroanatomical parcellation and classification performances of Monte Carlo Dropout (MCD), Deep Ensembles, and Evidential Deep Learning (EDL) architectures (specifically BPEN and DDEvENet) were analyzed. The algorithmic calibration and diagnostic reliability of the models were calculated using Expected Calibration Error (ECE), the Brier Score, and Negative Log-Likelihood (NLL) metrics. The evidential BPEN model demonstrated superior diagnostic calibration in MCI-to-Alzheimer's longitudinal progression classification, achieving 99.2% accuracy, a 0.985 F1 score, and an exceptionally low Brier score of 0.097, vastly outperforming standard Bayesian Neural Networks (53.1% accuracy) and baseline MCD (ECE ~0.185). In anatomical parcellation, DDEvENet increased the Dice Similarity Coefficient to 0.789 and Mean Recall to 0.804, surpassing Swin UNETR (0.731) and nnU-Net (0.749), while performing autonomous anomaly detection via Dirichlet evidence maps. Context-dependent multimodal fusion reduced overall NLLs by 13%. In automated classification abstention protocols, deferring diagnosis to a radiologist in the 34.2% of complex cases with high epistemic variance surged autonomous diagnostic accuracy from 80.8% to 95.5%. This uncertainty-driven triage mathematically bypassed the need for expensive FDG-PET scans in 92% of cases. The heterogeneity of neuroanatomical atrophy trajectories and partial volume effects strictly necessitate the mathematical quantification of uncertainty in MRI-based diagnoses. Evidential neuromodels not only restrict overconfident algorithmic errors but also quantify the epistemic boundaries created by cerebral lesions, providing physicians with highly reliable radiological anomaly maps. The integration of probabilistic deep learning architectures into clinical neuroinformatics ensures the optimal allocation of invasive multi-modal resources while establishing a calibrated ecosystem rooted in human-AI collaboration.

Disclosures: T. Morgül: None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.16/MM1

Topic: J.06. Computation, Modeling, and Simulation

Title: Machine learning classification suggests a greater effect of DMT-harmine on the temporal dynamics versus functional connectivity of the brain

Authors: *T. SMART[1], L. T. TRUJILLO[2];
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Abstract: Understanding the brain changes that result from the use of psychedelic compounds remains a challenge for neuroscience. Many studies have focused on functional connectivity changes of the brain, whereas other studies have examined changes in the brain's temporal dynamics, both of which appear to track corresponding alterations in perception, cognition, mood, and/or self-awareness. However, research on the relative effects of psychedelic compounds on brain functional connectivity and temporal dynamics is limited. Here, we addressed this gap by using machine learning (ML) to classify subacute brain states measured via functional magnetic resonance imaging (fMRI) following use of N,N-dimethyltryptamine (DMT) or a placebo. The fMRI blood oxygen dependent (BOLD) time series used was drawn from the open-access DMT-HAR-MED fMRI dataset (Egger et al., 2025, https://openneuro.org/datasets/ds006644/versions/1.0.1) in which 40 participants engaged in a three-day meditation retreat, with brain scans obtained before (T1) and after the retreat (T2). Twenty participants ingested a 120mg dose of DMT-harmine (DMT group), whereas the remaining twenty participants ingested a placebo (Placebo group) during the retreat. We then classified temporal and functional connectivity features of key resting state networks (RSNs) identified in the original dataset. Temporal features were defined as the T2 - T1 difference of the T1 and T2 RSN BOLD time series matrices. Functional connectivity features were defined as the T2 - T1 difference of the vectorized correlation matrices derived from the T1 and T2 RSN BOLD time series. Classification was implemented via a leakproof leave-one-subject-out support vector machine (SVM) algorithm. Results showed that data classification accuracy using temporal features was 78%, whereas accuracy based on connectivity was 65%. Classification based on temporal and connectivity features together yielded an accuracy of 72%, which suggests that connectivity might add noise to the feature set. We tentatively conclude from these findings that changes in the temporal features of the brain are more diagnostic for discriminating between the brain states of the DMT versus Placebo group than changes in the brain's connectivity. This suggests that although DMT use alters both temporal and connectivity features in the brain, the greater effect of DMT may be on the brain's temporal dynamics.

Disclosures: T. Smart: None. **L.T. Trujillo:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.17/MM2

Topic: J.06. Computation, Modeling, and Simulation

Title: Assessing Thalamocortical Circuit Modulation Induced by Vagus Nerve Stimulation Using Modulation Index

Authors: *Y. NAM;
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Abstract: Purpose Vagus nerve stimulation (VNS) is one of the most representative neuromodulatory treatments for patients with drug-resistant epilepsy who are not candidates for resective surgery. Although the therapeutic mechanism of VNS has not been fully elucidated, modulation of neuronal activity within the thalamocortical circuit has been proposed as an important mechanism. Several EEG biomarkers have been suggested to explain the effects of VNS; however, phase-amplitude coupling measured using scalp EEG has not been investigated in this context. Method We analyzed postoperative EEG recordings from 15 patients who underwent VNS implantation at the Division of Pediatric Neurology, Asan Medical Center, between 2017 and 2025. Epochs with VNS artifacts identified on electrocardiography were defined as the “on phase,” whereas epochs without VNS artifacts were defined as the “off phase.” Two-second epochs were extracted from each phase and underwent preprocessing. The modulation index (MI) was calculated between the phase of the delta(0.5-4Hz) band and the amplitude of the alpha(8-13Hz) band. The MI values were then normalized using surrogate testing. Statistical analyses were performed to identify significant differences between the two phases. Results When comparing the modulation index between the phase of the delta frequency band (0.5-4 Hz) and the amplitude of the alpha frequency band (8-13 Hz), the mean value across all channels was significantly higher during the “on phase” than during the “off phase” ($p = 0.026$). After correction for multiple comparisons using the false discovery rate, significant differences were observed in the F8 and T8 channels. Conclusion This study demonstrated a significant increase in delta phase-alpha amplitude coupling during the VNS “on phase” compared with the “off phase.” These findings suggest that VNS may induce immediate neurophysiological changes in patients with drug-resistant epilepsy by modulating cross-frequency interactions, potentially reflecting engagement of the thalamocortical circuit. Our findings suggest that scalp EEG-based phase-amplitude coupling analysis using the modulation index may serve as a noninvasive EEG biomarker for evaluating the neurophysiological effects of VNS.

Disclosures: Y. Nam: None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.18/Web Only

Topic: J.06. Computation, Modeling, and Simulation

Title: Class-conditional latent diffusion for dual-purpose EEG classifier augmentation and synthetic-data privacy

Authors: *T. WANG[1], Y. ZHAO[2];
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Abstract: Pretrained EEG foundation models compress recordings into low-dimensional embeddings, enabling two underexplored applications: class-conditional generative augmentation, and privacy-preserving synthetic data release. We test both on the Temple University Hospital Abnormal EEG Corpus (TUAB, binary normal/abnormal classification). Pipeline: finetune SleepFM (Nature Medicine 2026) end-to-end on TUAB; encode 163k 5-second windows into 128-d latents; train a class-conditional latent DDPM (5.5M-parameter MLP, 200 epochs); sample 163k synthetic latents 1:1 per class via DDIM-50; train classifiers on real-only (baseline), real+synthetic (augmented), and synthetic-only. Per-recording mean-pool evaluation matches the SleepFM$_1$ protocol.
We first attempted this on the Temple University Hospital EEG Events corpus (TUEV, 6-class event detection) but extreme class imbalance (98% background, 21 SPSW eval windows) precluded meaningful augmentation analysis (baseline Cohen's $\kappa = 0.024$ with augmentation collapsing onto the majority class). We therefore use TUAB as the canonical task.
Across 5 full-pipeline seeds on TUAB: augmentation improves AUC-PR by $+0.0040 \pm 0.0013$ (paired t-test $p<0.05$, 5/5 seeds positive); per-recording balanced accuracy reaches 0.836 ± 0.016, comparable to SleepFM$_1$'s reported pretrain-finetune number 0.83 (15 seeds). Notably, classifiers trained on synthetic-only latents match real-only utility on 4/5 seeds (BA 0.815 ± 0.050).
We probe this for privacy with three standard attacks: nearest-neighbor distance (T1) passes all 5 seeds; membership inference (T2) yields AUC0.504 ± 0.002 — much lower than the 0.55-0.70 reported for undefended CIFAR DDPM (Carlini 2022); patient re-identification (T3) passes on 3/5 seeds, with the 2 failures correlating with seeds where the upstream encoder or DDPM was weaker.
These results jointly support a "release synthetic latents instead of real "paradigm for medical EEG, with the caveat that formal (ε, δ)-DP requires DP-SGD on the diffusion stage (analysis in progress).

Disclosures: T. Wang: None. **Y. Zhao:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.19/MM3

Topic: J.06. Computation, Modeling, and Simulation

Support: BD2 Discovery grant, cycle 3 (MPI)

Title: Validation of dynamic functional connectivity approaches in detecting and predicting cognitively relevant states

Authors: *Z. WAN[1], C. LYNCH[2], I. ELBAU[3];
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Abstract: Cognition is widely thought to involve dynamic state-like processes, but conventional functional connectivity (FC) analyses assume a static network configuration. Dynamic functional connectivity (dFC) captures time-varying interregional correlations, enabling tests of whether cognitive states correspond to FC reorganizations. However, network dynamics captured by dFC can be prone to noise and difficult to interpret in terms of corresponding cognitive activities. To validate whether states captured by dFC are cognitively relevant or predominated by noise, we applied sliding-window K-means clustering and Hidden Markov Modeling (HMM) to the MyConnectome dataset (one adult male scanned repeatedly over >1 year during resting and task fMRI). This dataset allowed comparison between captured states and performed tasks, where tasks serve as proxy for cognitive states, and provided enough repeat scans for session-level randomized train-test splitting. States detected by each method were mapped onto cognitive tasks based on the predominant training-data task during each state. State-specific FC matrices (and parcel-wise mean signals for HMM) were matched to test data to predict tasks. While both methods recovered task structure in training data, only HMM generalized to held-out data. Across 20 randomizations with 10 specified states, states detected by both methods matched task labeling (5 tasks and 1 resting) well in training data (mean K-means sensitivity = 0.85, specificity = 0.99; mean HMM sensitivity = 0.70, specificity = 0.98). In testing data, only HMM performed well (mean K-means sensitivity = 0.42, specificity = 0.89; mean HMM sensitivity = 0.68, specificity = 0.95). Task-specific FC matrices were highly similar between the two methods for the same tasks (mean r = 0.99) and were only moderately different across tasks (mean r = 0.78). Parcel-wise mean signals captured by HMM across tasks were different (Friedman $p < 0.01$), suggesting that HMM's edge in out-of-sample prediction may come partly from identifying state-specific regional activation pattern alongside FC reorganization. These results suggest HMM captures cognitively relevant states that are reliable and reproducible in out-of-sample within-subject data. Consistent with literature, FC reorganizations during task activities are modest. Additionally, different cognitive activities may share the same states as defined by FC reorganizations only. Thus, FC reorganization alone may be insufficient to define cognitive state transitions, requiring complementary consideration of parcel-wise mean signal patterns as well.

Disclosures: Z. Wan: None. **C. Lynch:** None. **I. Elbau:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.20/MM4

Topic: J.06. Computation, Modeling, and Simulation

Support: American Parkinson Disease Association (APDA) 1053521
UM Frankel Innovation Initiative
Udall Parkinson's Foundation Research Center of Excellence

Title: CLEARNet and Autoencoder-Based Feature Discovery for DBS Local Evoked Potentials

Authors: *P. S. LAKSHMANAN[1], E. BENCE[1], E. GADZIC[1], A. HESTON[2], K. CHOU[2], K. CHEN[3], E. L. LEVIN[3,4], D. K. LEVENTHAL[2,5,6], E. OPRI[1,2];
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Abstract: Deep Brain Stimulation (DBS) is an established therapy for diseases such as Parkinson's Disease (PD). DBS alleviates motor symptoms by delivering electrical stimulation to deep brain regions such as the subthalamic nucleus. Yet, the exact mechanisms are unknown. Recent studies have revealed a novel biomarker called DBS Local Evoked Potentials (DLEPs), also known as ERNAs, that could potentially help understand mechanisms, and provide greater insights into functional mapping. However, due to the presence of stimulation artifacts, DLEPs are difficult to recover. Additionally, the features of DLEPs that can be used clinically to improve targeting and functional outcomes are still not fully understood. We apply deep-learning techniques to attempt to close these gaps.

First, to address the issue of stimulation artifacts, we developed a novel system called CLEARNet, that uses either a Convolutional Neural Network (CNN) or a Dense Neural Network (DNN). The models predict stimulation artifacts from raw local field potentials (LFPs) and predict stimulation artifacts. Both models were trained on raw LFP data collected from 16 subjects undergoing bilateral STN implantation surgery. LFPs were recorded non-stimulating contacts in response to burst stimulation of 1mA at 130Hz (10 pulses per burst). On the hold out test-set, the relative root mean squared error (RRMSE) of CLEARNet on the hold out test set was 0.1757 for the CNN, and 0.1515 for the DNN.

To assess the robustness of the artifact recovery in the absence of prominent evoked DLEPs, CLEARNet was also validated on LFP data collected from essential tremor (ET) subjects undergoing thalamic DBS targeting, as thalamic stimulation does not evoke DLEPs. CLEARNet was able to successfully predict stimulation artifacts regardless of subjects, contacts and disease differences.

Second, we used an autoencoder to identify latent representations of DLEP morphology. Average DLEPs were extracted from LFPs recorded from 15 subjects using established pipelines. A dense autoencoder was trained on DLEPs and its latent spaces were analyzed. Training, validation and testing were performed on groups of different subjects chosen at random. Reconstruction error plateaued with a six dimensional latent space, at an MSE of 0.290. Spearman correlation of each feature and latent dimension was calculated. The top features were entropy, peak to peak amplitude and gamma band average. These results support a deep-learning based pipeline for DLEP artifact recovery and feature discovery, supporting feasibility of direct ROI-based electrode localization with implications for clinical functioning mapping.

Disclosures: P.S. Lakshmanan: None. **E. Bence:** None. **E. Gadzic:** None. **A. Heston:** None. **K. Chou:** None. **K. Chen:** None. **E.L. Levin:** None. **D.K. Leventhal:** None. **E. Opri:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant NIDCD-R00-DC018051
NIH Grant NIDCD-R01-DC020960
NIH Grant NIDCD-F32-DC022145

Title: Invariant correlation: a general and straightforward method to quantify invariance in time-varying neural signals

Authors: *J. M. HICKS[1], D. BOEBINGER[1], K. V. NOURSKI[2], M. A. HOWARD, III[3], C. M. GARCIA[4], T. WYCHOWSKI[5], W. H. PILCHER[6], S. V. NORMAN-HAIGNERE[7];
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Abstract: Recognizing information in natural stimuli is challenging because sensory inputs for different instances of the same feature often vary substantially. Successful recognition thus requires neural systems to generate representations that are invariant to such variation, posing a fundamental computational challenge for sensory coding. Much remains unknown about how sensory systems code invariant information in complex, temporally dynamic stimuli such as speech, in part due to methodological challenges in measuring and modeling invariance from noisy, time-varying neural responses. Here, we introduce the “invariant correlation”, a straightforward and general method for directly quantifying the strength and temporal dynamics of invariance from time-varying neural signals and computational models. We demonstrate its utility by quantifying invariance to acoustic variation in neural representations of phonemes using spatiotemporally precise intracranial recordings from human auditory cortex. Our method successfully revealed substantial diversity in the strength and dynamics of invariance across the human auditory cortex and across different phonetic features within individual electrodes. We illustrate how many of these empirically measured patterns can be explained by applying the same analysis to the predictions from a simple computational model based on spectrotemporal tuning in a cochleagram representation of sound. Although we focus here on speech, the invariant correlation is a broadly applicable tool for characterizing the organization and

computational mechanisms underlying invariant representations of dynamic stimuli across sensory modalities.

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Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.22/MM6

Topic: J.06. Computation, Modeling, and Simulation

Title: A Meta-Analytical Framework to Enhance Replicability in Neurobehavioral Phenotyping in Mice

Authors: J. SUCHOVIC, V. D. KNICKERBOCKER, T. LASTER, J. OSGOOD, K. PERRON, N. STROUD, C. WISE, J. WOTTON, ***Z. BICHLER**;
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Abstract: Variability in experimental design, protocol implementation, and underpowered studies continues to limit the replicability of reported neurobehavioral phenotypes in mice. At the same time, the routine use of diverse mouse strains further underscores the need for standardized, harmonized reference datasets. To address this challenge, we leveraged the large and continuously expanding dataset generated by The Jackson Laboratory's Neurobehavioral Phenotyping Core since 2019. This resource comprises mice assessed under rigorously harmonized protocols, controlled environmental conditions, and standardized operator procedures. Using aggregated multi-assay data, we established strain-specific and age-stratified reference ranges for key motor and activity-related phenotypes. Our analytical framework included composite score generation, inter-assay correlation mapping, and cross-modal concordance analyses to assess redundancy and discriminative sensitivity across widely used behavioral assays and their specific variables. Using C57BL/6J as a benchmark strain, we identified assays with the greatest sensitivity to age- and sex-related effects, estimated empirically supported group size thresholds according to relative expected effect sizes, and evaluated inter-assay relationships to distinguish complementary versus redundant measures. Together, these analyses provide a practical framework for selecting robust phenotypes and designing efficient, data-driven behavioral pipelines with maximum statistical power. Ultimately, this work aims to enhance reproducibility, support more strategic and ethical study design, and promote alignment with the 3Rs principles (Replacement, Reduction, Refinement) in *in vivo* behavioral research. **Acknowledgement**: The authors gratefully acknowledge the contributions of all current and former staff members of the Neurobehavioral Phenotyping Core at the Center for Biometric Analysis, whose work was essential in generating the data underlying this study.

Disclosures: J. Suchovic: None. **V.D. Knickerbocker:** None. **T. Laster:** None. **J. Osgood:** None. **K. Perron:** None. **N. Stroud:** None. **C. Wise:** None. **J. Wotton:** None. **Z. Bichler:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR338.23/MM7

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R21NS135482

Title: Two-Timescale Integration of Scalp EEG and iEEG for Dynamic Whole-Brain Network Inference in Epilepsy

Authors: *S. YANG[1], F. LIU[2];
[1]Rutgers Univ., Newark, NJ; [2]school of systems and enterprises, Stevens Inst. of Technol., HOBOKEN, NJ

Abstract: Epileptic brain networks evolve across nested temporal scales: rapid directed interactions unfold within individual discharges, while broader functional and pathological regimes transition more slowly over time. Conventional static or single-timescale models may therefore either oversmooth transient interactions or produce unstable estimates from short windows. This challenge is compounded by the complementary limitations of electrophysiological recordings: scalp electroencephalography (EEG) provides broad coverage but limited source resolution, whereas intracranial EEG (iEEG) captures focal activity with high spatial precision but samples only selected regions. We developed a two-timescale switching state-space model that integrates simultaneous scalp EEG and sparse iEEG to infer state-dependent whole-brain directed networks. Slow transitions between network regimes are modeled with a hidden Markov process, while fast interactions are represented by state-specific multivariate autoregressive dynamics. Sequential iEEG-then-EEG Kalman filtering constrains latent source estimation, and sparse expectation-maximization jointly estimates brain states and networks. In simulations with known connectivity, sparse iEEG improved network recovery over scalp-only and conventional two-stage pipelines, showing that focal measurements can reduce ambiguity in whole-brain network inference. At 40% iEEG coverage, multivariate autoregressive and Granger-based network AUROC reached 0.658 and 0.653, versus 0.536 and 0.538 for scalp EEG alone, with state accuracy of 1.000. In ten patients with drug-resistant epilepsy and simultaneous recordings, the model identified spike-related states with balanced accuracy of 0.772, and top-ranked Granger connectivities showed strong clinical concordance (CC) with independently identified clinical regions (Granger CC@10=1.000). This suggests that sparse intracranial measurements can anchor whole-brain estimates of distributed epileptiform network organization beyond focal localization. Generalizability was further supported in an independent working-memory cohort (n=15), where inferred states aligned with encoding and maintenance (accuracy=0.818) and captured significant phase-dependent reversals in temporal/auditory-

hippocampal and cortical-subcortical information flow. Overall, multimodal, two-timescale modeling can recover shared principles of pathological and physiological network reconfiguration, providing an interpretable framework for dynamic whole-brain mapping and clinically relevant hypotheses about distributed epileptogenic networks.

Disclosures: S. Yang: None. **F. Liu:** None.

Poster

PSTR338: Statistical and Machine Learning Methods for Neural Data

Location: WCC Halls A-C

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Program #/Poster #: PSTR338.24/MM8

Topic: I.06. Social Cognition

Title: Multimodal Neural and Physiological Signatures of Real-World Smartphone Engagement

Authors: *V. KAGATHARA[1], P. MISHRA[2], S. R. GANDHI[3], T. K. GANDHI[4];
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Abstract: The ubiquity of smartphone usage necessitates a comprehensive understanding of its impact on human neurophysiology. While behavioral observations provide insights, integrating concurrent neural and physiological monitoring is essential for a holistic perspective in ecologically validated, naturalistic paradigms rather than artificial, stimulus-based laboratory setups. We present a multimodal dataset and a deep learning framework for decoding interaction-specific physiological signatures during smartphone use. 23 participants (ages 20-32, 8 females) were recorded simultaneously with 64-channel EEG, wearable eye-tracking, photoplethysmography (PPG), and galvanic skin response (GSR) while freely engaging with their most-used smartphone application, short-form video (n=14), mobile gaming (n=7), or reading(n=2), followed by a standardized passive baseline. All data streams were synchronized via TTL triggers and organized in BIDS format (OpenNeuro: ds007537). To decode behavioral engagement from these recordings, we developed the Brain-Body Spatio-Temporal Transformer (BB-STT), integrating multi-scale temporal convolution, spatial self-attention over EEG electrodes, and cross-modal attention fusion. The BB-STT achieved 83.51% accuracy in distinguishing smartphone vs. non-smartphone activity and 74.13% in three-class classification (video vs. gaming vs. baseline), outperforming conventional baselines by 19.45 F1 points. Leave-one-subject-out evaluation (84.32% accuracy; AUC: 86.73%) confirmed cross-subject generalization, indicating population-level signatures. Interpretability analyses using SHAP, permutation importance, and spatial attention maps revealed a two-stage physiological hierarchy. Device-context separation (smartphone vs. non-smartphone) was driven mainly by eye-tracking gaze depth, a geometric effect of shifting gaze from a monitor to a handheld screen, and supported by occipital EEG gamma activity. Within smartphones, scrolling and gaming differed in pupil dilation and central EEG gamma/beta activity (C1, CP1, TP9), indicating distinct arousal

and cognitive-motor demands. Architectural ablation confirmed cross-modal attention as the critical mechanism, improving accuracy by 16.74 points. Our data demonstrate that naturalistic smartphone engagement produces distinct, cross-modal physiological signatures. By leveraging a tiered sensing framework, we enable high-fidelity behavioral classification, establishing a powerful, passive methodology for future applications in digital health monitoring and neuro-ergonomic assessment.

Disclosures: V. Kagathara: None. **P. Mishra:** None. **S.R. Gandhi:** None. **T.K. Gandhi:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.01/MM9

Topic: J.07. Data Analysis and Statistics

Title: An application of machine learning using nearest centroid classifier with image datasets for open-set recognition

Authors: *H. C. YUAN[1], M. CHAO[2];
[1]Independent Lab., San Marino, CA; [2]Independent Lab., Rancho Palos Verdes, CA

Abstract: This poster investigates applying machine learning using the Nearest Centroid Classifier. This method works well in in high dimensional and low sample environments and this feature of nearest centroid classifier is a natural fit for neuroscience and neural data. For example, in many neuroscience experiments and research, datasets are in the form of 2-dimensional images. To apply nearest centroid classifier, centroids are computed from all pixels of known images and test images are classified as belonging to the nearest centroid. This poster will also investigate the use of open-set recognition in conjunction with the nearest centroid classifier to allow determining a presented open-set image as new or unknown. As researcher Walter J. Scheirer in his characterization of open-set recognition put it: “In addressing general object recognition, there is a finite set of known objects in myriad unknown objects, combinations and configurations - labeling something new, novel or unknown should always be a valid outcome. This leads to what is sometimes called "open-set" recognition, in comparison to systems that make closed world assumptions or use "closed-set" evaluation”. Nearest Centroid Classifier is selected in this investigation of open-set or unknown image rejection because of its use of all the pixels of an image as a feature vector without additional processing to select or derive features, and for direct geometric interpretation of Euclidean distance of an unknown image to a known image centroid as a measure of association of an unknown image to a known image. The distance is transformed by the softmax function to a probability between 0 and 1 where higher probability indicating more correlation to a known image centroid and lower probability indicating less correlation (potentially unknown) to a known image centroid. The Nearest Centroid Classifier training requires only computing the mean vector or centroid for each class without additional computation for density or covariance estimation. Decision

schemes and logic will be explored for best strategy to classify a known image and reject an unknown image. Processing will use monte carlo methods for the classification and rejection performance assessment. This poster will present an example of applying machine learning using the nearest centroid classifier in the field of face recognition for "open-set" recognition and unknown face rejection with the Yale Extended B face dataset.

Disclosures: H.C. Yuan: None. **M. Chao:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.02/MM10

Topic: J.07. Data Analysis and Statistics

Support: NSF DMS 2324962
FSU-CRC Seed grant

Title: NeuroSeq: A Functional Network Method for Analyzing Sets of Neural Spike Trains

Authors: *G. OWANGA[1], R. VINCIS[2], R. BERTRAM[3];
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Abstract: A major challenge in neuroscience is understanding how the dynamic ensemble-level neural activity gives rise to perception, cognition, and behavior, despite the apparent irregularity of individual spike trains. Increasing evidence suggests that neural activity evolves by structured, transiently stable patterns known as metastable states, which may represent a fundamental principle of cortical computation. Here, we introduce NeuroSeq, a functional network method for analyzing sets of neural spike trains that identify and track neural state transitions directly from spike-train data without assumptions about the number of states. NeuroSeq operates across three complementary scales. Applying NeuroSeq to neural recordings, we recover reproducible state transitions, recurring state families, and structured transition patterns that correspond with stimulus delivery and behavioral events. The framework uncovers both short-timescale state changes and long-timescale organizational structure that are difficult to detect using established approaches. These results show the utility of NeuroSeq for revealing metastable states that is applicable for both short and long time spans. To facilitate broad adoption, we developed NeuroSeq GUI, a cross-platform graphical interface that provides an end-to-end pipeline from raw spike trains to interpretable neural state sequences.

Disclosures: G. Owanga: None. **R. Vincis:** None. **R. Bertram:** None.

Poster

PSTR339: Data Analysis: Software Tools II

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.03/MM11

Topic: J.07. Data Analysis and Statistics

Support: NIH RO1AG072513
NIH T32NS115667

Title: How to Organize an Overwhelming Amount of Data: An Introduction to SQL

Authors: *C. J. BOUCHER[1,2,3,4], B. J. GLUCKMAN[1,2,3,4,5];
[1]Ctr. for Neural Engin., [2]Cross Disciplinary Neural Engin. Training Program, [3]Engin. Sci. and Mechanics, [4]Grad. Program in Neurosci., Pennsylvania State Univ., University Park, PA;
[5]Neurosurg., Pennsylvania State Univ. Col. of Med., Hershey, PA

Abstract: With increasingly stronger and more accessible computing power, neuroscience has entered an era of large-scale data acquisition. Modern experiments often combine cellular and molecular measurements with continuous behavioral and electrophysiological recordings, generating terabytes of data within days. Combined with growing data-sharing requirements, laboratories without extensive software development expertise often rely on commercial platforms with limited flexibility and scalability. Our laboratory has collected more than 240 TB of longitudinal behavioral and electrophysiological data across the lifespan of experimental animals. Managing datasets at this scale requires precise organization, rapid accessibility, and standardized metadata tracking. To address these challenges, we developed a data management pipeline using a relational database management system (RDBMS), SQL, to organize high-volume experimental data and associated metadata. This database framework tracks experimental procedures, animal identification and husbandry records, file locations, cohort information, and processing status across multiple experimental modalities. By defining hierarchical relationships between datasets, animals, experiments, and derived outputs, the pipeline enables rapid database queries, automated processing workflows, and streamlined preparation of datasets for analysis and sharing. Although optimized for longitudinal animal recordings, this framework provides a generalized and scalable approach for organizing biologically relevant datasets across diverse experimental paradigms. We present example use cases demonstrating implementation of SQL-based database pipelines for high-throughput neuroscience research.

Disclosures: C.J. Boucher: None. **B.J. Gluckman:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.04/MM12

Topic: J.07. Data Analysis and Statistics

Title: Open-Source Packages for Neural Data Analysis, Statistical Modeling, and Perceptual Stimulus Synthesis

Authors: *G. VIEJO[1], S. C. VENDITTO[2], W. F. BRODERICK[3], E. BALZANI[3];
[1]Flatiron institute, New York, NY; [2]Neurosci., [3]Ctr. for Computat. Neurosci., Flatiron Inst., New York, NY

Abstract: Modern neuroscience increasingly depends on computational tools for analyzing large-scale neural recordings, developing quantitative models, and generating experimental stimuli. To support these needs, we present three complementary open-source Python packages : Pynapple, NeMoS, and Plenoptic.Pynapple is a lightweight library for neurophysiological data analysis centered on standardized representations of time series and time intervals. The package provides efficient data structures for spike trains, behavioral variables, and experimental epochs, along with commonly used neuroscience analyses such as tuning curves and cross-correlograms. Since its public release in 2022, Pynapple has seen growing community adoption. To address the need for multimodal visualization of neural and behavioral data, we developed Pynaviz, a GPU-accelerated visualization framework tightly integrated with Pynapple data structures.NeMoS (NEural MOdelS) is a GPU-accelerated statistical modeling library designed to simplify the development and application of encoding models for neural activity. The package provides a flexible and extensible implementation of generalized linear models (GLMs), compatible with both Pynapple and scikit-learn. Recent developments include GLM-hidden Markov models (GLM-HMMs) and categorical GLM. Ongoing work focuses on extending the framework to generalized additive models (GAMs), point-process GLMs for high-resolution functional connectivity inference and Gaussian Process (GP) regression.Plenoptic is a library for model-based synthesis and analysis of perceptual stimuli. By generating stimuli that optimize or manipulate model representations, Plenoptic enables researchers to probe the computations performed by models of perception and neural processing. These synthesized stimuli can be used to generate experimentally testable predictions and to evaluate competing theories of sensory coding. Recent work includes support for penalty terms that bias synthesis towards stimuli with desired image properties.Together, these projects promote reproducibility and transparency by providing tools for data representation, visualization, statistical modeling, and stimulus synthesis.

Disclosures: G. Viejo: None. **S.C. Venditto:** None. **W.F. Broderick:** None. **E. Balzani:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.05/MM13

Topic: J.07. Data Analysis and Statistics

Title: EasySort: a browser-based graphical interface for code-free spike sorting

Authors: *S. WEISS[1,2];
[1]Stempel, Max Planck Inst. for Brain Res., Frankfurt am Main, Germany; [2]rentaSpike, Frankfurt am Main, Germany

Abstract: Extracellular electrophysiology routinely yields recordings from hundreds to thousands of channels, and spike sorting—assigning detected action potentials to putative single units—is an essential but technically demanding step. SpikeInterface (SI) has unified the field by wrapping more than twenty sorters and dozens of file formats behind one Python interface, yet using it still requires scripting, environment management, and knowledge of each sorter's parameters, a real barrier for the many experimentalists who do not program. While AI can help with technical setup, it cannot yet replace a human looking at the data and deciding which preprocessing, drift correction, and sorter-parameter tuning will achieve meaningful results. EasySort is a platform-agnostic, browser-based graphical application that offers a complete, code-free spike-sorting pipeline built on SI. It delivers the same validated algorithms through a guided, no-code browser interface whose core idea is a human-in-the-loop visual check at every step: the user sees probe wiring, raw vs filtered traces, estimated motion, sorted units and quality metrics, and confirms each before moving on.
EasySort auto-detects and reads over twenty acquisition formats, including SpikeGLX, Open Ephys, Intan, Neuralynx, and Neurodata Without Borders (NWB). Probe configuration offers automatic Neuropixels mapping and draws on the ProbeInterface-library (Neuropixels, Cambridge NeuroTech, NeuroNexus, SINAPS), with support for custom probe files. Preprocessing follows SI standards, includes bandpass filtering, global and local common-average referencing, automatic bad-channel detection, and destriping. Drift correction with motion visualization allows the user to easily test and apply different motion correction algorithms prior to sorting. EasySort runs sorters natively via SI, locally via MATLAB, or in containers via Docker, all while allowing parameter editing. After sorting, it computes standard quality metrics, applies automated curation that removes excess or duplicated spikes and redundant units, and exports results to Phy, NWB, or Zarr. Manual curation with SI-GUI is also included. The application runs natively on Windows and Linux, with macOS support currently in testing.
By turning a scripting-heavy workflow into a guided interface while preserving SI's validated, transparent backend, EasySort lowers the barrier to reproducible spike sorting and helps standardize analysis within and across laboratories.

Disclosures: S. Weiss: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); rentAspike.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.06/MM14

Topic: J.07. Data Analysis and Statistics

Support: NIH STTR 1R41DA064482

Title: Deep Learning-Based Pose Estimation Reveals Fine-Scale Behavioral Dynamics During Variable Pavlovian Conditioning in Mice

Authors: *A. ENGLISH[1], B. LAND[2], N. STELLA[4], M. R. BRUCHAS[3];
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Abstract: We present a high-resolution behavioral analysis framework leveraging computer vision pose estimation to characterize how mice engage with conditioned stimuli (CS), unconditioned stimuli (US), and reward delivery during a prolonged Pavlovian conditioning paradigm with systematically varied task contingencies. Traditional approaches to Pavlovian conditioning typically rely on coarse, event-aligned measures such as approach latency, port entries, or trial-averaged response rates. These are vitally important features, especially for alignment with neural recordings, but limit insight into how learning reshapes moment-to-moment action strategies in the animal's behavior. To address this, we applied BioSyft's tracking and behavioral modeling to continuously quantify posture, movement kinematics, and action sequences across a 10-week longitudinal experiment. Mice were trained on a Pavlovian task in which CS–reward contingencies were systematically altered across sessions, including training, changes in sucrose concentration (3%, 10%, and 30%), probabilistic reward omission (including a 50% omission condition), and extinction. For this study, a CS (house light), US (tone), and reward (sipper-sucrose) were utilized with standardized ITI's. Using deep learning–based pose tracking, we extracted continuous behavioral features capturing locomotion, orienting, head and snout dynamics, and micro-movements surrounding CS, US, and reward epochs. We quantified how these behavioral signatures evolved across training and contingencies. Our results show that Pavlovian learning produces structured, time-locked behavioral changes extending beyond simple approach or consumption measures. We identify behavioral motifs associated with CS anticipation, reward expectation, and reward receipt. Together, this work demonstrates that deep learning–driven pose estimation provides a scalable framework for dissecting learned behavior at fine temporal resolution, revealing how behavioral organization adapts to changing reward contingencies in ways not captured by conventional approaches.

Disclosures: A. English: A. Employment/Salary (full or part-time):; BioSyft Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioSyft Inc.. F. Consulting Fees (e.g., advisory boards); BioSyft Inc. **B. Land:** F. Consulting Fees (e.g., advisory boards); BioSyft Inc. **N. Stella:** F. Consulting Fees (e.g., advisory boards); BioSyft Inc. **M.R. Bruchas:** F. Consulting Fees (e.g., advisory boards); BioSyft Inc..

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.07/MM15

Topic: J.07. Data Analysis and Statistics

Title: BrainGPS AI: An AI-Assisted Platform for Visualizing and Personalizing Brain Stimulation Targets Across Neurological and Psychiatric Disorders

Authors: *Z. ZHANG[1], X. KANG[2], J. KONG[1];
[1]Mass Gen. Hosp., Charlestown, MA; [2]LIGHT HOPE LLC, Arlington, MA

Abstract: Background:The rapid expansion of neuroimaging and neuromodulation research has generated a large body of evidence identifying potential brain stimulation targets across neurological and psychiatric disorders. However, translating this information into clinical practice remains challenging. We developed BrainGPS AI, an interactive neuroinformatics platform designed to visualize, organize, and personalize brain stimulation target selection using neuroimaging evidence and artificial intelligence. Methods: BrainGPS AI integrates a curated database of 128 neuroimaging-derived potential cortical targets identified through large-scale coordinate-based meta-analyses spanning 18 neurological and psychiatric disorders, with functional decoding of each target performed using Neurosynth Compose. The platform incorporates target coordinates, anatomical regions, functional network assignments, and transdiagnostic circuit relationships. Each target is traceable to its source publication (PMID/DOI). An interactive visualization module enables users to explore disorder-specific targets on three-dimensional (MNI152) brain representations and identify overlapping targets across disorders. In parallel, an AI-assisted recommendation engine utilizes symptom-to-circuit mappings and transdiagnostic network information to prioritize candidate stimulation targets based on individual symptom profiles rather than diagnostic labels alone. Results: BrainGPS AI provides rapid access to disorder-associated stimulation targets and supporting neurobiological evidence through an intuitive visual interface, eliminating the need for manual review of multiple publications and reference tables. The platform supports both diagnosis-based and symptom-based workflows. The AI recommendation system further refines target selection by integrating primary symptom domains with associated neural-circuit signatures (literature-derived associations), generating personalized target rankings and highlighting shared circuit mechanisms across disorders. Conclusions: BrainGPS AI represents a scalable framework for translating large-scale neuroimaging evidence into candidate brain stimulation targets for research and hypothesis generation across multiple stimulation modalities (e.g., TMS, tACS, and scalp acupuncture).

Disclosures: Z. Zhang: None. **X. Kang:** A. Employment/Salary (full or part-time):; LIGHT HOPE LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Equity in Light Hope LLC. **J. Kong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Equity in MNT and BTT startup, inventor on granted patent US 2018/0339148 plus pending applications.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.08/MM16

Topic: J.07. Data Analysis and Statistics

Support: NIH P50HD118603

Title: DAPR MAPR: A Modular, User-friendly, Scalable Toolkit to Harmonize and Map Neurorehabilitation Data

Authors: *O. MARIN-PARDO[1], M. H. KHAN[2], K. J. LOOMIS[1], S. CHAKRABORTY[1], S. ARZA[3], S.-L. LIEW[1,4];
[1]Chan Div. of Occup. Sci. and Occup. Therapy, [2]Neurosci. Grad. Program, [4]Stevens Neuroimaging and Informatics Inst., [3]USC, Los Angeles, CA

Abstract: Aggregating rehabilitation datasets across multiple research studies might enable large-scale analyses to detect subtle rehabilitation improvements. This would allow the implementation of novel artificial intelligence (AI) methods to make accurate cross-sectional and longitudinal predictions of rehabilitation outcomes. However, combining multisite data to create sufficiently large datasets is challenging due to inconsistent rules and parameters governing data storage, organization, and sharing. For example, non-uniform variable names and conventions across research teams make it time-consuming to manually harmonize and verify aggregated data (i.e., ensure that all variable names and their associated values and codes represent equivalent information). Previous efforts have aimed to increase the interoperability of healthcare data across institutions (e.g., the Observational Medical Outcomes Partnership [OMOP] Common Data Model [CDM]). However, current solutions such as OMOP do not fully incorporate many neurorehabilitation research variables; a recent analysis from our group demonstrated that approximately 50% of rehabilitation variables are not captured by OMOP. Here, we present a toolkit developed to address the data harmonization challenges and needs specifically for neurorehabilitation research. With assistance from AI agents, we curated a scalable human- and machine-readable data dictionary that captures the extent and granularity reflected in neurorehabilitation studies and interventions, for example, including total, subscale, and item-level assessments of motor, cognitive, and sensory function, as well as quality-of-life evaluations, demographics, and clinical data from stroke research. Additionally, this dictionary includes cross-reference maps to existing OMOP concepts. More than 1100 rehabilitation variables from neurorehabilitation research from the ENIGMA Stroke Recovery database were included in the curated dictionary. Finally, we developed an interactive web application to match unstandardized names to the standardized dictionary and to provide a correspondence key with associated metadata. In this work, we present a software toolkit to assist neurorehabilitation researchers in easily harmonizing multisite data and mapping it to existing CDMs, accelerating data standardization efforts, and increasing the interoperability of rehabilitation data. Future work will incorporate dictionary variables from additional medical conditions (e.g., Parkinson's Disease, Cerebral Palsy), CDMs, and data types (e.g., time-series data).

Disclosures: O. Marin-Pardo: None. **M.H. Khan:** None. **K.J. Loomis:** None. **S. Chakraborty:** None. **S. Arza:** None. **S. Liew:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.09/MM17

Topic: J.07. Data Analysis and Statistics

Title: SpikeSSL: Generalizable Spike Inference Across Calcium Indicators

Authors: *C. YUE[1], Y. ZHANG[2];
[2]Life Sci., [1]Tsinghua Univ., Beijing, China

Abstract: Spike inference from two-photon calcium imaging remains difficult to generalize across calcium indicators because each indicator produces distinct fluorescence dynamics and noise characteristics. We present SpikeSSL, a dynamics-aware deconvolution framework that combines bidirectional IIR state-space layers with indicator- and trace-conditioned modulation to improve robustness across recording conditions. SpikeSSL is evaluated on public paired fluorescence-spike datasets under both in-domain and leave-one-indicator-out settings, where it improves accuracy over existing supervised methods. We further augment training with biophysically simulated traces that vary calcium kinetics, spike statistics, nonlinear responses, drift, and noise, reducing the cross-indicator generalization gap. These results support SpikeSSL as a generalizable framework for calcium-imaging spike inference.

Disclosures: C. Yue: None. **Y. Zhang:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

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Topic: J.07. Data Analysis and Statistics

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National Cancer Institute (NCI) through the Case Comprehensive Cancer Center Support Grant (P30CA043703)

Title: DeepFaceMouse enables scalable prediction of large-scale brain activity from facial dynamics in mice

Authors: *K. OZDEMIRLI[1], T. L. CONNOR[5], K. KIM[2], E. UNLU[2], M. LACIN[6], M. MALDONADO[2], A. OKSUZ[7], B. D. TRAPP[3], J. D. LATHIA[8], M. YILDIRIM[4];
[1]Cleveland Clin. Res., Arlington, VA; [2]Neurosci., [3]Cleveland Clin. Res., Cleveland, OH; [4]Neurosci., Cleveland Clin. Res., shaker heights, OH; [5]Res. Svc., Cleveland Dept. Veterans Affairs Med. Ctr., Cleveland, OH; [6]LRI Neurosciences, Cleveland Clin., Cleveland, OH; [7]Computer Sci., Case Western Reserve Univ., Cleveland, OH; [8]Learner Res. Inst., Dept. of Stem Cell Biology, Lerner Res. Inst., Cleveland, OH

Abstract: Facial movements are closely linked to large-scale brain activity and provide a window into internal neural and behavioral states. However, extracting reliable orofacial features from long and heterogeneous recordings remains a major bottleneck, particularly in large-scale and disease-focused studies. Existing pose-estimation tools often require extensive manual refinement or fail to generalize across experimental conditions. As multimodal studies increasingly aim to link behavior to the brain-wide neural dynamics, there is a need for automated and scalable approaches that are robust across datasets. DeepFaceMouse addresses this challenge by providing a high-precision, computationally efficient, and easily deployable framework for scalable orofacial tracking and brain-behavior analysis.

Disclosures: K. Ozdemirli: None. **T.L. Connor:** None. **K. Kim:** None. **E. Unlu:** None. **M. Lacin:** None. **M. Maldonado:** None. **A. Oksuz:** None. **B.D. Trapp:** None. **J.D. Lathia:** None. **M. Yildirim:** None.

Poster

PSTR339: Data Analysis: Software Tools II

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Topic: J.07. Data Analysis and Statistics

Support: This work was supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) (RS-2026-25472883).

Title: High-Resolution Intracranial Neuronal Activity from Less-Invasive, Low-sampling EEG via Cross-Modal Neural Representation Learning

Authors: *J. LEE[1,2,3], J.-W. LEE[4,5], H. KANG[3,4,2];
[2]Interdisciplinary Program in Bioengineering, Col. of Engin., [3]Integrated Major in Innovative Med. Science, Col. of Medicine,, [4]Dept. of Biomed. Engineering, Seoul Natl. Univ. Col. of

Med., [1]Seoul Natl. Univ., Seoul, Korea, Republic of; [5]Dept. of Electrical Engin. and Computer Sci., Daegu Gyeongbuk Inst. of Sci. and Technol. (DGIST), Daegu, Korea, Republic of

Abstract: Skull EEG enables less-invasive neural monitoring, but skull and soft tissue attenuate high-frequency and spatially focal cortical signals. In contrast, ECoG directly records cortical surface dynamics, including interictal spikes and seizure bursts. We hypothesized that ECoG activity not visible in skull EEG remains partly encoded in low-frequency phase, amplitude, inter-channel temporal structure, and population-level dynamics. To test this, we developed NeuroU-Net, a machine-learning EEG-to-ECoG reconstruction framework trained on simultaneous multichannel skull EEG and epidural ECoG from kainic-acid-induced seizure mice. Wild-type C57BL/6 male mice aged 7-8 weeks were used; sex differences were not assessed. Analyses included a 25-kHz EEG/25-kHz ECoG cohort (n=7) and a true low-sampling 2-kHz EEG/25-kHz ECoG cohort (n=3). Recordings were split into 7-min training and 3-min testing segments. An encoder-decoder model reconstructed ECoG from EEG alone, while raw EEG and six neural-network architectures served as controls. Performance was assessed using automated metrics: spike-detection F1 score, Pearson correlation, waveform correlation, and PCA-based representational similarity. Statistics used Friedman and Wilcoxon signed-rank tests with Benjamini-Hochberg FDR correction. Before reconstruction, ECoG showed greater band-pass-filtered power and higher total spike rates than EEG in both cohorts, confirming attenuation of fine-scale cortical activity in skull recordings. In the 25-kHz/25-kHz cohort, NeuroU-Net reconstructed ECoG with high fidelity, achieving F1=0.444±0.068, Pearson r=0.814±0.059, waveform r=0.870±0.054, and PCA similarity=0.722±0.075. It outperformed comparator models in correlation, waveform similarity, and representation geometry ($q \leq 0.015$). After EEG downsampling to 2 kHz, NeuroU-Net remained superior to raw EEG for F1 score (0.432±0.079 vs. 0.148±0.069), Pearson r (0.809±0.067 vs. 0.440±0.091), and waveform r (0.837±0.066 vs. 0.585±0.102; $q \leq 0.027$), and exceeded baseline models for F1 score and correlation ($q \leq 0.031$). In the true 2-kHz cohort, it recovered more ground-truth-matched spike timestamps than raw EEG (582 vs. 127 total; 194±172 vs. 42±22 per mouse). These findings suggest that skull EEG may retain recoverable information about fine-scale cortical dynamics despite attenuation. Transforming skull EEG into ECoG-like representations may enhance less-invasive seizure monitoring and support brain-machine interfaces by integrating complementary strengths of invasive and less-invasive neural recording modalities.

Disclosures: J. Lee: None. **J. Lee:** None. **H. Kang:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.12/MM20

Topic: J.07. Data Analysis and Statistics

Title: A high-recall pipeline for detecting extracellular purine release events in biosensor imaging data

Authors: *Z. GAO[1], A. D. UMPIERRE[2], D. N. ANDERSON[3];
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Abstract: Extracellular purinergic signaling plays a critical role in damage signaling during seizure activity, but quantitative analysis of fluorescent biosensor recordings remains limited by manual event annotation. Frame-by-frame review of long recordings is time-consuming and subjective, creating a bottleneck for non-biased, high-throughput screening. Here, we developed an assisted-annotation pipeline that pre-screens recordings and flags candidate events for expert review. The pipeline combines bidirectional frame-differencing detection optimized for slow, diffusive purinergic signals, spatiotemporal clustering with extended temporal windows, and supervised classification to identify candidate release events. We validated the approach on two-photon fluorescence recordings (1800 frames, 1.01 Hz) from acute brain slice preparations. A dataset of 341 manually annotated events generated independently from the algorithm output served as the ground truth. The pipeline recovered 317 of 341 events, achieving 93% event-level recall. Notably, a subset of algorithmically flagged candidates that did not match the manual annotation set were confirmed upon re-review to represent genuine events, suggesting that high-recall automated screening can aid in identifying events initially missed by human observers. After collapsing redundant detections, the workflow shifts from exhaustive frame-by-frame search to targeted evaluation of algorithmically flagged candidates, reducing total annotation time from 30-40 minutes to approximately 10-12 minutes per recording. An integrated desktop application (FluoroTrack) provides interactive review, ROI correction, and TP/FP labeling in a streamlined workflow, enabling consistent event identification and systematic extraction of quantitative kinetic metrics. This framework supports scalable screening of extracellular purinergic biosensor signals in hyperexcitability models, enabling experimental designs that would be impractical under fully manual workflows.

Disclosures: Z. Gao: None. **A.D. Umpierre:** None. **D.N. Anderson:** None.

Poster

PSTR339: Data Analysis: Software Tools II

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Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

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Topic: J.07. Data Analysis and Statistics

Support: NIH/NIDCD R01 DC014701
NIH/NIDCD R01 DC019124
NSF EFMA-2223811

Title: From segmentation to behavior: agentic feature engineering in Annolid for interpretable animal action classification

Authors: *C. YANG, T. A. CLELAND;
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Abstract: Automated analysis of animal behavior requires mapping behavioral representations onto meaningful actions. Pose-based representations are widely used but labor intensive. We developed an agent-assisted workflow in Annolid, an open source platform for animal segmentation, labeling, tracking, and behavior analysis, to ask whether segmentation polygons can provide interpretable representations of posture, movement, and behavior while reducing keypoint annotation burden. We compared visual weak labels from GPT-5.5, pose markers, pose markers plus velocity, Annolid polygon geometry, and Annolid polygon temporal features, using Macro F1 (0.0-1.0, higher is better) as the main classification metric. In mouse open field videos scored for supported rearing, unsupported rearing, and grooming (Blau, 2024; Sturman, 2020), Annolid single mouse polygon temporal features achieved a Macro F1 of 0.725 across 40,515 behaviorally categorized frames without any manual keypoint labeling. (Automatically derived features included boundary points, area, centroid, perimeter, motion index, temporal convolutional modeling, and 25-frame smoothing). The source pose estimation workflow (Sturman, 2020) tracked 13 mouse body points plus arena landmarks and trained the OFT DeepLabCut model from 120 manually labeled pose training frames, corresponding to approximately 2,160 manual point annotations. A temporal convolutional network trained by Blau (2024), using these pose-derived features, plus inferred velocity, achieved a Macro F1 of 0.766. In head-fixed fruit fly videos (Blau, 2024; Schaffer, 2023), Annolid inference based on one frame manually annotated with three rough polygons achieved a Macro F1 of 0.754 on held-out data, compared with 0.91-0.94 from a pose estimation workflow requiring 14,168 manual point annotations across 26 videos. Visual weak labels from GPT-5.5 performed poorly in both cases (Macro F1 of 0.257 for mouse and 0.212 for fly).These results show that segmentation masks, like pose trajectories, can serve as interpretable substrates for behavioral classification. Annolid acts as a human-in-the-loop container for detection, segmentation, tracking, and temporal classification models, including Grounding DINO, SAM-family segmentation, Cutie video object tracking, and TCN behavior classifiers. By combining editable polygons, pose features, temporal dynamics, calibrated classifiers, and transparent performance reports, Annolid provides a reproducible framework for identifying behavioral states within animal videos while reducing manual annotation burden. Annolid is freely available at https://cplab.science/annolid.

Disclosures: C. Yang: None. **T.A. Cleland:** None.

Poster

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Support: HHMI
ASAP

Title: Beyond the soma: a whole-cell instance segmentation benchmark and annotation framework for neurons and glial cells in microscopy data

Authors: J. MAR'I[1], A. ATES[2], M. ABT[1], R. BARNOWSKI[1], D. VAN VALEN[1];
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Abstract: Neuronal and glial morphology underlies cognition and neurodegenerative disease, yet the standard neural tracing reconstruction method reduces cells to skeletons, discarding the volumetric detail that fine morphology comprises. Instance segmentation preserves richer morphometry but cannot scale without data. There is a need for a resource that offers dense whole-cell instance masks for both neurons and glia in brain tissue, precluding generalizable segmentation models. To close this gap, we present an open-source, model-agnostic benchmark and semi-automated annotation framework for training and evaluating instance segmentation across the morphological and contextual complexity of brain tissue. The benchmark aggregates five metadata-standardized datasets from multiple institutions with around 36K 2D and 3D z-stacked confocal images containing ~525K neurons, microglia, and astrocytes, spanning mouse, macaque, and iPSC-derived tissue across regions including hippocampus and cortex. Annotations are produced with an in-house napari 2D/3D plugin optimized for confocal and large multiplexed CODEX data, whose flood-fill algorithm enables semi-automatic labeling of both nuclear and whole-cell compartments. The framework yields ~40K 2D/3D instance masks ready for model development and reduces annotation time from 5+ hours to ~30 minutes per image. Because every mask derives from this single reproducible pipeline, the resource is internally consistent and community-extensible, and it is served openly through a searchable, Zarr/SQL-backed web portal for browsing, visualization, and download; the plugin is released for labeling new data.

Disclosures: J. Mar'i: None. **A. Ates:** None. **M. Abt:** None. **R. Barnowski:** None. **D. Van Valen:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH Grant U24NS120057-05
NIH Grant R24MH117295-04

Title: Conversational AI agents for converting neurophysiology data to NWB and reanalyzing the DANDI Archive

Authors: *P. W. ADKISSON-FLORO[1], S. WEIGL[1], A. TRAPANI[1], L. TAUFFER[1], H. MAYORQUIN[1], E. HENNESTAD[2,1], B. DICHTER[1];
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Abstract: Neurophysiology data sharing depends on two labor-intensive steps that remain bottlenecks for most labs: converting heterogeneous acquisition formats into a standardized form, and reanalyzing shared datasets once they are public. The Neurodata Without Borders (NWB) standard and the DANDI Archive provide the infrastructure for both, yet conversion and reanalysis still demand substantial software engineering expertise. We present two open-source agentic skills that use large language models to guide these workflows through natural conversation while keeping a scientist in the loop at each decision.
The first skill, nwb-convert, acts as a conversion specialist. It leads an experimentalist through experiment discovery, direct inspection of raw acquisition files, metadata collection, temporal synchronization, and generation of a documented, pip-installable conversion repository built on NeuroConv and PyNWB. The agent draws on a knowledge base of 68 NeuroConv interface specifications, canonical repository templates, patterns distilled from roughly 20 real conversions, and NWB best practices, and supports extracellular and intracellular electrophysiology, calcium imaging, segmentation, and behavior. Conversions are validated with NWB Inspector and uploaded to DANDI. The skill runs from the command line or bundled inside the NWB GUIDE desktop application.
The second skill, analyzing-dandi-datasets, supports reanalysis. It discovers relevant dandisets, streams NWB files with LINDI and remfile rather than downloading them, and builds modular, reproducible pipelines with Pynapple for phenomena such as directional tuning, place fields, and population dynamics. The agent works only with real archived data, validates each data stream before analysis, and reviews every generated figure for quality.
Together these tools move conversion and reanalysis from bespoke engineering projects toward conversational, reproducible workflows, broadening participation in open neurophysiology. Both skills are released under an open-source license at github.com/catalystneuro/claude-skills.

Disclosures: P.W. Adkisson-Floro: None. **S. Weigl:** None. **A. Trapani:** None. **L. Tauffer:** None. **H. Mayorquin:** None. **E. Hennestad:** None. **B. Dichter:** None.

Poster

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Program #/Poster #: PSTR339.16/MM24

Topic: J.07. Data Analysis and Statistics

Title: AMBER: Automated Marble Bury Evaluation and Reporting

Authors: *F. MALATO[1], D. YORK[1], L. HARSHMAN[1,2], L. P. SOWERS[1,3,2], J. M. STABER[1]; [1]Stead Family Dept. of Pediatrics, Carver Col. of Med., Univ. of Iowa, Iowa City, IA; [2]Carver Col. of Med., Iowa Neurosci. Inst., Iowa City, IA; [3]VA Ctr. for the Prevention and Treatment of Visual Loss, Iowa City, IA

Abstract: The marble burying test is commonly used to evaluate repetitive (compulsive-like), anxiety-like, and general exploratory/digging behaviors in mice by exploiting an instinctive

innate tendency of rodents to dig and bury objects in their environment. In this test, twenty marbles are arranged in a regular grid over a layer of clean bedding, after which a mouse is allowed to freely explore the environment for thirty minutes. Traditionally, the test is scored by multiple blinded evaluators who quantify the number of buried marbles at the end of the session. More recently, the advent of machine learning has enabled more sophisticated analyses, including characterization of burying bouts and temporal behavioral dynamics from video recordings. However, currently available, open-source methods remain highly sensitive to the experimental setup, often require time-consuming data annotation, and omit several sources of behavioral information. To address these limitations, we propose AMBER, an AI-driven automated evaluation pipeline for the marble burying test. Our pipeline includes independent modules for marble & mouse segmentation and tracking, marble occlusion detection, and mouse behavior classification, resulting in an extremely detailed analysis of test dynamics. The pipeline is built upon a mixture of open source technologies such as Segment Anything 3 and DeepLabCut, well-known AI architectures, such as Siamese and Modern Hopfield Networks, and novel models designed specifically to pursue our goals. The core principles behind the design of our pipeline include: i) provide objective and quantifiable evaluation metrics for the marble burying assay; ii) reduce the reliance on human evaluators thereby minimizing personal bias and measurement uncertainty; iii) maintain an open, modular, and efficient pipeline, to promote re-usability and adaptability to a wide range of computational settings. We evaluate the effectiveness of our pipeline by comparing its outputs with scores obtained from human evaluators on the same experimental sessions. Our preliminary results suggest that our automated pipeline can reliably quantify marble burying behavior. Furthermore, the modular design of our approach naturally supports the integration of additional behavioral tests with minimal modification.

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Poster

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Program #/Poster #: PSTR339.17/MM25

Topic: J.07. Data Analysis and Statistics

Title: Benchmarking preprocessing and automating neuron selection in two-photon calcium imaging

Authors: T. SILVA[1], S. PAJEVIC[2], ***D. PLENZ**[3];
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Abstract: Two-photon imaging with genetically encoded indicators (GECI, GEVI) enables cell-specific recording of neuronal activity with a relatively high spatial and temporal resolution.

Converting the raw fluorescence into reliable single-cell traces remains a bottleneck: indicator-dependent kinetics, slow calcium relaxation, and imaging noise make region-of-interest (ROI) detection and spike inference error-prone, and the standard remedy—manual curation—does not scale to the thousands of neurons in a large field of view across many experimental conditions. We address this by automating and benchmarking preprocessing along two dimensions: (1) signal-to-noise improvement through denoising and spike inference via deconvolution of the original calcium indicator traces; (2) reliable neuronal identification, in which candidate ROIs are curated so that only viable, active neurons are kept for analysis. For (1), we compare two denoising techniques—DeepInterpolation and wavelet shrinkage—between them and against no denoising, and three deconvolution schemes: OASIS (native to Suite2p), CASCADE, and MLspike. For (2), recognizing limitations in the default Suite2p ROI selection, we introduce an automated cell-selection scheme that trains a supervised classifier on human-curated datasets to identify active neurons, improving both sensitivity and specificity. As features, we use multiple sets derived from ROI/soma shape and neural activity traces. Our training set comprised over a thousand individually curated datasets, most containing 100-400 active neurons. We benchmark how accurately individual cells and their spiking activity can be recovered, using both real two-photon recordings and simulated datasets with known ground truth. In the simulations we use a set of experimentally obtained ROIs and simulate spiking activity, convolved with a given calcium probe and adding different amounts of noise. Our results (1) show that using DeepInterpolation denoising and MLspike deconvolution was judged as the best spike estimation protocol, and (2) that our automated cell selection greatly outperforms the default Suite2p ROI detection, achieving accuracy close to 90% (with f1 score of 0.8, and ROC AUC=0.95), and also identify the best-performing classification features among hundreds that we use. Using a highly reduced set of the most important features, we still obtain reliable estimates. This integrated approach enhances downstream analyses of neural population dynamics, paving the way for more robust, scalable calcium imaging workflows by minimizing the need for human curation.

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Poster

PSTR339: Data Analysis: Software Tools II

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Title: Surface Mapping of Cerebellar Microstructure in Infancy

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Abstract: The cerebellum undergoes its most rapid growth during the first years of life, developing densely packed folia surrounding the arbor vitae that support motor and cognitive function. Despite the highly convoluted nature of the cerebellar cortex, cerebellar analyses are still often performed volumetrically in the adult MNI space. Here, we demonstrate that subject-specific surface-based analysis improves cerebellar mapping.
Using data from the Baby Connectome Project (389 scans), we mapped cerebellar myelination (T1w/T2w ratio) using three pipelines: (1) subject-specific surfaces in native space followed by surface-based registration to the MNI cerebellar surface, (2) sampling on the MNI cerebellar surface following volumetric registration to MNI space, and (3) SUIT-based flatmap projection following volumetric registration to MNI space. SUIT blurred cortical detail (green arrows) and sampled beyond the cerebellar boundary due to registration misalignment (red arrows), producing artefacts in right Crus I (blue arrows). MNI surface sampling recovered sharper cortical detail but remained susceptible to registration mismatch. In contrast, native-surface sampling preserved fine-grained cortical detail without introducing artefacts.
Relative to the whole-cerebellum developmental reference (black), SUIT produced implausibly high Right Crus I values, inconsistent with Crus I's role as a higher-order region with protracted maturation. In contrast, native-space sampling followed by surface-based registration improved anatomical correspondence across subjects and yielded substantially better GAMM fits (R^2 = 0.65) than MNI surface sampling (0.59) and SUIT (0.49).

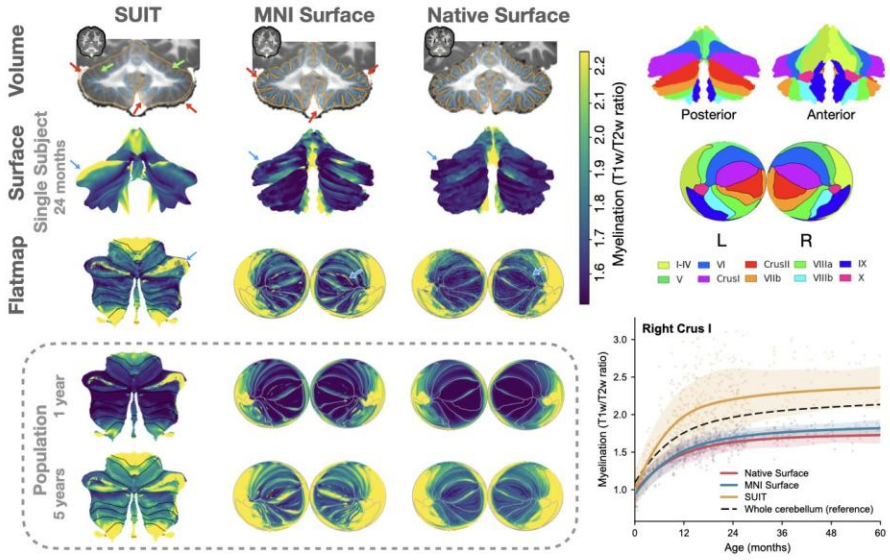


Figure. Surface–volume mismatch blurs cortical detail (green arrows) and causes data sampling beyond the cerebellar boundary because of registration errors (red arrows), leading SUIT to produce apparent artefacts in right Crus I (blue arrows). The MNI surface-sampling pipeline improves cortical sharpness but remains susceptible to registration mismatch. In contrast, subject-space surface mapping better preserves cerebellar cortical geometry. Population results are obtained using generalized additive mixed models (GAMMs).

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Poster

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S10 OD032223
S10 OD034205

Title: Disentangling Spurious and Genuine Correlations in Resting-State Neurovascular Coupling

Authors: *D. P. AKSENOV, N. SERDYUKOVA, E. DOUBOVIKOV, K. ESTRADA, A. ARDASHEV, A. DROBYSHEVSKY;
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Abstract: Resting-state neurovascular coupling is often inferred from correlations between spontaneous neural activity and hemodynamic signals. However, both neural and vascular signals contain strong slow fluctuations, making it difficult to distinguish true coupling from correlations that arise by chance. In this study, we examined the relationship between spontaneous cortical tissue oxygen dynamics and electrophysiological activity in awake rabbits using simultaneous recordings of tissue oxygen, local field potentials, and single-unit activity from somatosensory cortex. To address the problem of autocorrelation, we compared the observed neural-oxygen relationships with surrogate data that preserved key statistical properties of the original signals while disrupting their temporal alignment. This approach showed that many apparent correlations between neural activity and tissue oxygen could be explained by chance structure in the data. After this correction, robust coupling was mainly observed between tissue oxygen and delta-band local field potential activity, while higher-frequency bands did not show reliable coupling. At the single-neuron level, only a sparse subset of neurons showed significant relationships with tissue oxygen, suggesting that resting oxygen fluctuations are not driven by uniform changes in overall firing rate. Instead, they appear to reflect activity in selected neuronal subpopulations. These findings highlight the importance of rigorous statistical controls when studying spontaneous neurovascular coupling. They show that resting vascular signals can be linked to specific neural dynamics, but that much of the apparent coupling can be overestimated without accounting for autocorrelation. More broadly, this work provides a framework for identifying meaningful neural contributions to resting hemodynamic fluctuations and improves interpretation of spontaneous vascular signals measured in neuroimaging studies.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R21DC021756

Title: Toward identification of auditory disorders with an automated machine learning analysis of evoked potentials

Authors: *D. PERRENOUD, K. MOON, A. KAMERER;
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Abstract: Identifying the underlying cause of hearing loss is difficult, as many pathologies may look identical on behavioral assessments. Auditory evoked potentials (AEPs) measure electrical activity along the auditory pathway and therefore could detect a wide range of sensory and neural disorders. Traditional analysis of AEPs, however, depends on manual or simple local-extrema-based peak identification that is tedious, loses quality in noisy recordings, and limits interpretable data to a few major hallmarks. We developed an automated Gaussian-mixture model (GMM)-based feature extraction technique for AEP waveform analysis that runs without manual intervention and accurately fits human responses. The present study expands the approach to animal species and assesses whether it is more efficient at detecting pathology than the traditional analysis. The GMM technique was applied to five animal models of auditory pathology: (1) a mouse model of Charcot-Marie-Tooth disease (CMT1A, CMT1E); (2) mice given a Trk receptor inhibitor; (3) mice exposed to damaging noise levels; (4) a guinea pig model of Ménière's disease, and (5) a budgerigar model of neuropathy. The analysis detects local extrema and applies a latency-informed filtering step to identify and label AEPs, fitting a GMM to the waveform via gradient descent optimization as a steppingstone toward fully learned, neural network-based feature extraction. The technique extracted a set of structural hallmarks for each detected AEP creating a profile used to generate a predictive model of disease. GMM fit quality was excellent across species with median RMSE normalized to max amplitude ranging from 1% (guinea pigs) to 2.9% (mice) for high level stimuli and reduced (to <5%) as expected as stimulus level decreased. Preliminary analyses show the GMM technique replicates findings of traditional analyses, such as systematically delayed AEP latencies in CMT1E mice relative to wildtype, but finds additional features in diseased AEP profiles, such as shallower curvature in early AEPs of CMT1A mice and the auditory nerve compound action potentials in guinea pigs with Ménière's disease compared to wildtypes/shams. The AEP profiles created by the technique provide exponentially more data that improve disease prediction in the examined animal models. As the technique does not require the user to have *a priori* knowledge of AEP morphology or coding and it generalizes across species and recording parameters, this is the next step toward a standardized, reproducible AEP analysis that scales to large datasets and lays the foundation for development of precision treatment for hearing loss.

Disclosures: D. Perrenoud: None. **K. Moon:** None. **A. Kamerer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intelligent Hearing Systems.

Poster

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Program #/Poster #: PSTR339.21/MM29

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NIH Grant NS106244

Title: Coding-free, lab-scale infrastructure for spike sorting

Authors: K. S. PATEL, R. A. TIKIDJI-HAMBURYAN, *M. T. COLONNESE;
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Abstract: Centralization and automation of data analysis pipelines help distribute computational resources efficiently, reduce investigator workload, standardize methodology, and shorten the integration time for new investigators. Post-recording preprocessing and spike-sorting of high-channel count probes (e.g., Neuropixel, SiNAPS, Neuronexus)- requiring large storage needs and specialized hardware, as well as parameters optimized for by probe, region, and experiment-is a methodology that will benefit from lab-level centralization.Here we present Spike Sorting Lab Hub (SSLH), a web-based infrastructure designed to simplify and streamline spike-sorting workflows. SSLH allows users to collect and manage sorting parameters for specific recordings (sorting pipelines), apply these pipelines to new datasets, distribute workloads across multiple computing nodes (workers), and monitor sorting progress in real time. SSLH is implemented as a lightweight Django-based web server that can be integrated into Network-Attached Storage (NAS) platforms, such as TrueNAS, as a standalone Docker container. This architecture provides flexibility and scalability, enabling SSLH to operate efficiently on infrastructures ranging from a laboratory NAS with a single dedicated worker to large-scale spike-sorting farms or cloud-based environments. A key strength of SSLH is its modular design. Functionality is encapsulated into independent Django applications, allowing future expansion and customization without disrupting existing components. This approach improves maintainability, simplifies deployment, and supports long-term platform development.At the time of submission, SSLH is undergoing beta testing. Its source code is publicly available on GitHub under the GNU General Public License (GPL). Future functionality includes automated merging of recordings and downsampling. By combining accessibility, scalability, and modularity, SSLH lowers the technical barrier to high-quality spike sorting and promotes more consistent and reproducible analysis across complex electrophysiological datasets.

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

Poster

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NRF Grant No. 00450314
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Title: SPECTAR: Spike-Preserving Spectral Artifact Removal for Intracortical Microstimulation Recordings

Authors: *S.-H. KIM[1], M.-K. KIM[3], J.-W. SOHN[4,2];
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Abstract: Bidirectional neuroprostheses aim to restore sensation by delivering intracortical microstimulation (ICMS) while simultaneously recording neural activity, a closed loop that requires detecting spikes during ongoing stimulation. A major limitation of this approach, however, is that each stimulation pulse produces a large, pulse-locked artifact that can obscure neural spiking activity in the near post-stimulation period. Because this artifact is most severe in the first millisecond after each pulse (exactly when short-latency, stimulus-evoked spikes occur) suppressing it without distorting the overlapping neural signal has remained difficult. Here, we present SPECTAR, an artifact-removal algorithm designed to suppress ICMS artifacts while preserving spikes that overlap with stimulation pulses.For each pulse, SPECTAR builds an artifact estimate from the spectral structure shared across neighboring pulses and captures the remaining pulse-to-pulse variability with a low-rank basis. To avoid removing genuine spikes, this artifact basis is then made orthogonal to a spike subspace and refit so that spike-like components are excluded. We evaluated SPECTAR using ground-truth simulations derived from real ICMS recordings. Clean neural activity, spike waveforms, artifact profiles, and pulse-to-pulse artifact variability were estimated directly from these recordings. Artifact and spike sources were separated across fitting and testing pools to prevent leakage between model training and evaluation. Performance was compared with raw traces, template subtraction, ERAASR1, and ERAASR2 using threshold-based spike detection, residual artifact power, waveform similarity, and latency error.Across 600 channel-trials collected from four recording conditions, three independent trials, and 50 channels, SPECTAR consistently improved spike recovery relative to existing artifact-removal methods. SPECTAR achieved a mean F1-score of 0.534, compared with 0.355 for ERAASR2 and 0.278 for template subtraction, while reducing spike-band residual RMS to 12.4 μV. The advantage was largest for spikes within 1 ms of stimulation onset, where SPECTAR reached an overlap F1 of 0.460, compared with 0.268 for ERAASR2.

Recovered spike waveforms remained highly similar to ground truth (r = 0.838), and spike timing was preserved with low latency error (MAE = 0.038 ms). Overall, these results suggest that SPECTAR can improve neural signal recovery during ICMS by balancing artifact suppression with preservation of overlapping spikes, supporting its potential use in sensory neuroprostheses experiments.

Disclosures: S. Kim: None. **M. Kim:** None. **J. Sohn:** None.

Poster

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Topic: J.07. Data Analysis and Statistics

Support: MUR PRIN 2022 BHISTROT Grant: 2022YZRF4E

Title: Automated detection and quantification of dendritic varicosities in histaminergic neurons from confocal microscopy images

Authors: *E. BRUNO[1,2], A. COSTA[3], C. MAGLIARO[1,2], G. PROVENSI[3], M. PASSANI[4], N. VANELLO[1,2];
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Abstract: The histaminergic (HAergic) neurons of the tuberomammillary nucleus (TMN) are the unique neuronal source of histamine in the brain, extending their projections to virtually all major encephalic regions. Histamine is predominantly released via varicosities scattered along neuronal fibers, with synthesis and release modulated by H3 autoreceptors. Functional heterogeneity within the HAergic population in response to stress suggests that distinct subpopulations may engage different brain circuits depending on behavioural demands. Here, we introduce a tool for the 3D morphometric analysis of HAergic dendritic varicosities, aimed to investigate structural plasticity induced by stress. Adult histidine decarboxylase (Hdc)-Cre mice received bilateral injections of pAAV-Syn-ChR2(H134R)-GFP into the TMN to transduce HAergic neurons. Confocal stacks of immunolabeled hypothalamic coronal sections (20 µm thick) were acquired (Nikon A1, 40x objective). Neuronal structures were reconstructed through SENPAI, a segmentation algorithm exploiting image intensity and Hessian-based second-order derivatives to detect tubular and protruding neuronal structures. The dendritic skeleton was estimated from the volumetric segmentation and HAergic varicosities were detected on the 3D neuronal segmentation using the Shape Diameter Function (SDF), which estimates local structural thickness to identify cross-sectional enlargements along the dendrite. By integrating the SDF values and skeleton radii into a Gaussian Mixture Model (GMM), two distributions were identified allowing to distinguish varicosities from the dendritic core; as a result, we could

characterize varicosity morphology and spatial distribution along the dendrite. The median varicosity radius was 1.35 µm (MAD: 0.24 µm) and varicosities density was 0.18 varicosities/µm. This framework provides a tool to understand whether prolonged stress induces morphological changes in HAergic dendritic varicosities, for which no reference values are currently available in literature.

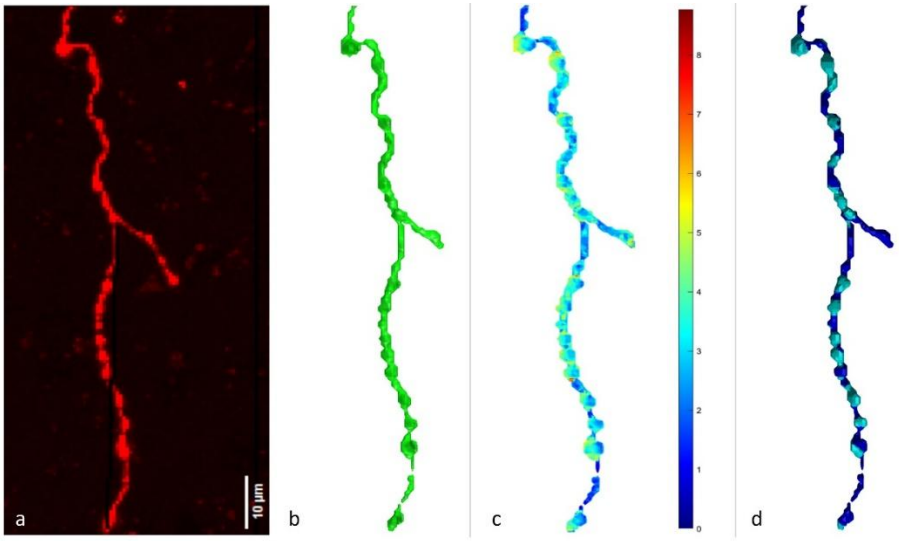


Figure 3D reconstruction and morphological analysis of a HAergic dendrite. (a) Maximum intensity projection of the original confocal image. Scale bar: 10 µm. (b) 3D segmentation of the dendrite. (c) SDF, color-coded by local structural thickness. (d) Varicosities detected via GMM.

Disclosures: E. Bruno: None. **A. Costa:** None. **C. magliaro:** None. **G. Provensi:** None. **M. Passani:** None. **N. Vanello:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.24/MM32

Topic: J.07. Data Analysis and Statistics

Title: Real-Time TMS-EEG Using Ultra-Flat Active Electrodes

Authors: *J. GRUENWALD, PhD[1], S. SIEGHARTSLEITNER[1,2], K. MAYR[1], **C. GUGER**[1]; [1]g.tec medical engineering GmbH, Schiedlberg, Austria; [2]Inst. of Computat. Perception, Johannes Kepler Univ., Linz, Austria

Abstract: Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) enables direct assessment of cortical excitability and connectivity via TMS-evoked

potentials (TEPs). However, conventional TMS-EEG workflows remain time-consuming, fragmented across multiple software tools, and often dependent on offline post-processing before signal quality and evoked responses can be evaluated. We present an integrated real-time TMS-EEG pipeline that covers the complete experimental workflow from montage creation to online TEP inspection. The system combines ultra-flat active electrodes with software modules for montage definition, impedance check, EEG quality control and acquisition, real-time TMS artifact handling and signal processing, and interactive topographic visualization. During setup, the selected montage guides cap preparation and impedance assessment; continuous EEG views allow the operator to verify signal quality before stimulation. During acquisition, incoming data are processed online and displayed as single trials and/or as evolving averages. The TEP viewer provides latency cursors for component inspection and scalp topographies whose colormap is updated according to the selected time cursor, enabling immediate spatial assessment of evoked activity without post hoc export.The workflow also integrates EMG channels for motor-threshold procedures. EMG activity can be visualized live, and thresholding tools provide immediate feedback for detecting motor evoked potentials and supporting stimulation-intensity adjustment. Thus, EEG quality, EMG responses, stimulation events, real-time preprocessing, and cortical evoked potentials can be monitored within one interface. In practical use, the complete workflow can progress from mounting the cap to examining interpretable TEPs in approximately 15 minutes, including montage setup, impedance verification, online EEG/EMG inspection, stimulation-triggered acquisition, real-time processing, and visualization of single-trial and averaged responses. By moving preprocessing and decay artifact removal into the acquisition loop, the platform reduces the delay between data collection and quality assessment, allows immediate troubleshooting, and supports reproducible TMS-EEG recordings. This real-time system makes high-quality TMS-EEG more efficient and accessible for research and clinical environments where rapid setup, online quality control, and immediate interpretation are essential.

Disclosures: J. Gruenwald: A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **S. Sieghartsleitner:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **K. Mayr:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.25/MM33

Topic: J.07. Data Analysis and Statistics

Support: Blux Inc.'s Internal Funding

Title: Leveraging Bevy ECS for High-Performance Digital Twin in Behavioral Neuroscience

Authors: *S. Z. WANG[1,2];
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Abstract: Background: Modern behavioral neuroscience increasingly relies on the integration of complex, multi-modal data streams. However, researchers face significant structural bottlenecks in laboratory data management, high-throughput processing, and the precise temporal synchronization of diverse modalities, such as behavioral tracking and neural activity recordings.
Methods: To overcome these limitations, we developed a high-performance, interactive digital twin system tailored for murine behavioral experiments. Built upon a robust Entity-Component-System (ECS) architecture, this framework moves beyond traditional monolithic software designs, treating experimental subjects, sensory inputs, and environmental variables as independent, concurrently updatable data nodes.
Results: This decoupled architecture inherently resolves temporal lag, enabling strictly synchronized, millisecond-level alignment across different sensory modalities. Crucially, the system achieves deep computational compatibility with in vivo calcium imaging, allowing for the seamless merging of spatial-behavioral phenotypes with real-time neural dynamics. Furthermore, the digital twin environment supports real-time logical control, enabling closed-loop experiments where dynamic environmental feedback is triggered instantly by specific behavioral or neural events. To accommodate the growing computational demands of modern neuroscience, the platform incorporates standardized, zero-overhead API interfaces designed specifically for seamless artificial intelligence integration. This allows downstream machine learning models to directly ingest, analyze, and infer from live experimental data streams without interrupting data acquisition.
Conclusions: By bridging the gap between raw multi-modal data collection and advanced computational modeling, this ECS-based digital twin provides a scalable, highly performant infrastructure. It not only standardizes laboratory data management but also paves the way for next-generation, AI-driven closed-loop behavioral research.

Disclosures: S.Z. Wang: A. Employment/Salary (full or part-time):; Blux Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blux Inc..

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.26/MM34

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R01NS116384

Title: DeepLabCut-Based Cognitive and Anxiety Behavior Analysis After Traumatic Brain Injury in Long-Evans Rats

Authors: *M. KIM[1], O. ANDERSON[1], G. NAIR[1], S. SHIMEALL[1], B. ZHANG[1], I. WILLIS[1], A. G. MACHADO[1,2], K. B. BAKER[1,3];
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Abstract: Traumatic brain injury (TBI) increases the risk of neuropsychiatric disorders, including persistent cognitive, behavioral, and emotional challenges. Pre-clinical behavioral assessments using animal models can evaluate interventions across cognitive, motor, and emotional domains. In quantifying ethological behaviors, manual human scoring remains the standard but is limited by scorer fatigue, variability, and inconsistent definitions of complex behaviors. DeepLabCut (DLC)-based approaches match the accuracy of traditional scoring while providing scalability and flexibility. Despite these advancements, DLC has not yet gained widespread adoption due to a lack of comprehensive validation against established behavioral measurement methods. Consequently, it is essential to first determine whether the DLC approach aligns with current behavioral knowledge compared with traditional human-scoring methods. In this study, we applied and evaluated a DLC-based behavioral analysis pipeline in the medial prefrontal cortex (mPFC)-controlled cortical impact (CCI) rodent model for TBI. The open field test (OFT), novel object recognition (NOR) test, and elevated plus maze (EPM) were used to assess locomotor, exploration, memory, and anxiety-like behaviors. 12 rats underwent longitudinal behavioral testing of the OFT and NOR test at four time points: pre-CCI and weeks 1, 2, and 4 post-CCI. At each post-injury time point, 3 rats were sacrificed to measure brain lesion volume. Thus, 12 rats were tested at pre-CCI and week 1, 9 at week 2, and 6 at week 4. 10 rats were tested on the EPM at pre-CCI and at week 5 post-CCI. Behavioral data were analyzed using manual scoring by three independent observers and a DLC-MATLAB pipeline operated by two operators, to assess reproducibility and reduce human-dependent variability. Behavioral changes were compared pre- and post-CCI while controlling for test disease severity, illumination, inter-task interval, and latency to onset. To validate the automated pipeline, two independently trained DLC models were compared with the ground truth, derived from the median values of three manual annotators, using Pearson correlation (r), TOST equivalence testing, ICC(2,1) absolute agreement, and Bland-Altman analysis. DLC models showed a strong linear association and high absolute agreement with the ground truth (median r = 0.97; ICC = 0.94). Two DLC models were highly consistent (median ICC = 0.99), exceeding human inter-rater agreement (median ICC = 0.93). These results support DLC-based approaches as reliable, scalable tools for quantifying post-TBI neuropsychiatric behaviors and developing TBI treatments.

Disclosures: M. Kim: None. **O. Anderson:** None. **G. Nair:** None. **S. Shimeall:** None. **B. Zhang:** None. **I. Willis:** None. **A.G. Machado:** None. **K.B. Baker:** None.

Poster

PSTR339: Data Analysis: Software Tools II

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Program #/Poster #: PSTR339.27/MM35

Topic: J.07. Data Analysis and Statistics

Support: R01NS117585
R01NS123154

Title: A dense-prediction U-Net framework resolves overlapping and low-amplitude synaptic events across brain slices and human organoids

Authors: *Y. SHU[1], J. ZHANG[2], X. CHEN[2], M. C. DADARLAT[3], Y. YANG[2];
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Abstract: Accurate quantification of postsynaptic currents (EPSCs/IPSCs) is fundamental for deciphering neural circuits and synaptic pathology. However, detecting minute events in low-signal-to-noise recordings is heavily based on time-consuming, subjective manual screening. Existing deep learning solutions remain constrained by window-level classification paradigms, where temporal resolution is fundamentally tied to sliding stride, creating prohibitive computational costs for high-frequency overlapping signals. Here, we introduce an end-to-end, fully convolutional 1D U-Net framework that decouples temporal resolution from inference stride via chunk-wise dense prediction and an overlap-add strategy. This approach achieves exceptional sensitivity for low-amplitude peaks and rapid inference speeds. To handle complex real-world kinetics, the architecture exhibits exceptional robustness. Its pointwise probability mapping accurately dissociates highly overlapping events, a capability we rigorously quantified using a novel, dynamically adaptive O-score metric. Simultaneously, it leverages dilated convolutions to seamlessly capture the slow long-range dynamics of IPSCs, maintaining high-throughput inference. Evaluated exclusively on highly heterogeneous real-world recordings rather than idealized simulations, the model achieved state-of-the-art performance in acute mouse brain slices. Furthermore, it demonstrated robust cross-scale generalization: models trained solely on mouse slices achieved zero-shot cross-preparation inference in human brain organoids and readily adapted to region-specific bursting dynamics in the mPFC via low-cost global fine-tuning. Packaged with a code-free graphical interface, this system provides a high-throughput, calibration-free paradigm to standardize synaptic event analysis across the neuroscience community.

Disclosures: Y. Shu: None. **J. Zhang:** None. **X. Chen:** None. **M.C. Dadarlat:** None. **Y. Yang:** None.

Poster

PSTR339: Data Analysis: Software Tools II

Location: WCC Halls A-C

Time: Wednesday, November 18, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR339.28/MM36

Topic: J.07. Data Analysis and Statistics

Support: HHMI

Title: An open-source analysis framework for multi-animal extracellular electrophysiology in freely interacting rodents.

Authors: *M. PROSKURIN[1], Y. PAN[2], D. G. TERVO[1];
[2]Janelia research campus, [1]Janelia Res. Campus, Ashburn, VA

Abstract: Brains evolved for social life. Recognizing individuals, anticipating their actions, cooperating, and competing all happen in the company of conspecifics. Yet systems neuroscience has historically measured neural activity one animal at a time in isolated chambers, leaving the brains-in-dialog that animals actually evolved to be largely unexplored. Recent advances now allow simultaneous extracellular recordings from many neurons across several freely-behaving animals interacting in a shared arena. The bottleneck has shifted to analysis. Each session yields electrophysiology data, multi-animal location tracking, and scored behavioral events from distinct acquisition systems on independent clocks. Existing one-animal toolkits lack clock alignment, cross-animal binning, partner-conditioned analyses, and multi-brain population methods. We introduce Ratcity toolkit, an open-source Python framework that ingests spike-sorted data, animal-resolved location tracking, and scored events; aligns electrophysiology and behavioral clocks; and exposes every animal's data through a unified shared-clock interface. Modules cover decoding of opponent identity, interaction outcome, and spatial position; PCA/UMAP/Rastermap population geometry; allocentric "social place fields" testing whether individual neurons encode the position of specific conspecifics; and a shared/unique subspace decomposition that captures coordinated dynamics neither brain shows alone. A Python API and interactive GUI provide scripted and point-and-click access. By unifying the multi-animal data plane and bundling cross-brain analyses that previously required custom implementation, Ratcity toolkit shortens analysis time. Applied to a 12-rat cohort (4 with wireless chronic Neuropixels) in a large arena, it supports analyses spanning quality control, partner-specific spatial coding, and inter-brain coupling. We are extending it to include analysis of social vocalizations, unsupervised social-behavior segmentation linked to neural activity, and detection of social-experience replay during rest as well as support of NWB data format. By making cohort-scale analysis routine, Ratcity toolkit aims to shift the field from studying isolated brains to studying brains as they evolved — in interaction with each other.

Disclosures: M. Proskurin: None. **Y. Pan:** None. **D.G. Tervo:** None.

Poster

PSTR339: Data Analysis: Software Tools II

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Program #/Poster #: PSTR339.29/MM37

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R24MH117295

Title: The growing DANDI ecosystem: new tools for exploring, searching, and reusing open neurophysiology and neuroimaging data

Authors: B. DICHTER[1], ***K. GUNALAN**[2], R. CHOUDHURY[4], J. NESBITT[4], M. VANDENBURGH[4], A. MACDONALD[5], I. C. TO[6], C. BAKER[5], D. JARECKA[3], Y. O. HALCHENKO[7], S. S. GHOSH[3];
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Abstract: The DANDI Archive (dandiarchive.org) is a BRAIN Initiative-supported platform for publishing and sharing cellular neurophysiology and neuroimaging data, hosting over 580 dandisets comprising 1.3 PB of electrophysiology, optical physiology, behavioral, and imaging data standardized in Neurodata Without Borders (NWB), BIDS, and OME-Zarr. Here we present recent advances across the DANDI ecosystem that make open data easier to discover, explore, and reuse. DANDI Atlas (atlas.dandiarchive.org) provides interactive 3D visualization of archive contents registered to standard anatomical atlases, allowing users to browse available data by brain region across species. A new AI-powered metadata assistant (medit.dandiarchive.org) streamlines dandiset curation by suggesting standardized metadata from uploaded files and free-text descriptions, improving metadata completeness and searchability. The archive's search functionality has been extended with structured query operators supporting filters on species, modality, file type, and subject counts, enabling precise programmatic and interactive discovery. For large-scale imaging data, integrations with Neurosift, Neuroglancer, and NeuroGlass enable in-browser visualization of multi-terabyte volumetric and neurophysiology datasets. Standardized processing pipelines, including robust spike-sorting workflows for extracellular recordings, are now run automatically on all qualifying assets. Example exploratory analyses (dandi.github.io/example-notebooks) are available as one-click Google Colab notebooks requiring no local setup. Ongoing standards development extends NWB and BIDS to cover microelectrode recordings as well as behavioral video and audio recordings and stimulus media. These tools are developed through a sustained collaboration among academic institutions (MIT, Dartmouth College), research software companies (CatalystNeuro, Kitware), Foundations (Flatiron) and the broader open source community, demonstrating a model for sustainable research infrastructure. Together, these advances lower the barrier to finding and reanalyzing public neurophysiology data, supporting reproducible neuroscience.

Disclosures: B. Dichter: A. Employment/Salary (full or part-time):; CatalystNeuro. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CatalystNeuro. **K. Gunalan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DataJoint. **R. Choudhury:** A. Employment/Salary (full or part-time):; Kitware. **J. Nesbitt:** A. Employment/Salary (full or part-time):; Kitware. **M. VanDenburgh:** A. Employment/Salary (full or part-time):; Kitware. **A. Macdonald:** None. **I.C. To:** None. **C. Baker:** None. **D. Jarecka:** None. **Y.O. Halchenko:** None. **S.S. Ghosh:** None.