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Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.01/D1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Fer family protein expression is restricted by inherited stem cell transcription factors to promote specific neuron differentiation

Authors: *K. C. DRAKE[1], C. Q. DOE[2];
[1]Biol. Dept., Univ. of Oregon, Eugene, OR; [2]Univ. Oregon, Eugene, OR

Abstract: Proper development of complex nervous systems relies on newly born neurons obtaining precise, unique cell identities. One of the main drivers of neuronal identity and differentiation is the initial suite of transcription factors (TFs) it inherits from its neural stem cells (NSC). In the *Drosophila* ventral nerve cord (VNC) neural stem cells have a well characterized pattern of differential TF expression that results in each post-mitotic neuron receiving its own spatial, temporal, and Notch$^{ON/OFF}$ identity. Through this process, each hemisegment of the VNC produces ~300 neurons with genetically unique TF combinations. While we know the TF code used by many of these neurons, how the combination of initially inherited TFs influences fate specification is still poorly understood. Our previous work identified a TF expressed in post-mitotic neurons: Fer3 (forty-eight related 3), which is tightly regulated by the three molecular mechanisms described above and is necessary for promoting expression of a downstream interneuron specific TF, Dbx. Using immunohistochemical staining and genetic manipulation, we have shown that the regulation of Dbx by Fer3 has a higher order regulation via the temporal TFs- only the early temporal identities inherited from the NSC are permissive to this function of Fer3, allowing Dbx to be expressed in the first few interneurons born but not in the later born neurons. Furthermore, preliminary data following up on this suggests that two other TFs in the same protein family (Fer1 and Fer2) also regulate these same genetic programs in completely different contexts (different spatial, temporal, and Notch identities). We are currently investigating how these inherited identities restrict Fer1 and Fer2 expression as well as how the same downstream programs operate differently in these different contexts. This work adds to the growing knowledge of how TF codes contribute to and define neuron differentiation and neurodevelopment.

Disclosures: K.C. Drake: None. **C.Q. Doe:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.02/D2

Topic: A.01. Neurogenesis and Gliogenesis

Support: BYU College of Life Sciences Grants on the Edge

Title: The Hox transcription factor mab-5 is necessary and sufficient for transcriptional differences between the left and right Q-derived neuron pairs in Caenorhabditis elegans

Authors: E. CHILD[1], T. BARNEY[2], E. DAVIS[2], M. LYMAN[2], S. BENNETT[1], A. ROLFSON[1], *S. R. TAYLOR[1];
[1]Cell Biol. and Physiol., [2]Neurosci. Ctr., Brigham Young Univ., Provo, UT

Abstract: Neurons display striking diversity in morphology and function. We have used the post-embryonic neurons derived from the left and right Q neuroblasts of *Caenorhabditis elegans* as a model to understand the generation of transcriptional diversity in the nervous system. The Q neuroblasts give rise to three pairs of neurons: the oxygen-sensing AQR/PQR and SDQR/SDQL neurons and the touch receptor neurons AVM/PVM. Single-cell RNA sequencing of adult animals revealed dozens of differentially expressed genes between the left and right neurons of each pair, including several genes encoding neuropeptides and neuropeptide receptors. Using confocal imaging of fluorescent reporter alleles, we have validated differential expression of several neuropeptides and the glutamate transporter *eat-4*. These patterns of differential expression are established in the first larval stage and persist into adulthood. We show that the Hox transcription factor *mab-5* is both necessary and sufficient for asymmetric expression of the neuropeptides *nlp-64* and *ins-17* in the SDQ neuron pair. Furthermore, *mab-5* is continuously required to maintain differential expression, since degradation of MAB-5 protein using the auxin inducible system after initial development results in de-repression of *nlp-64* in SDQL. Ectopic expression of *mab-5* in SDQR results in the loss of *nlp-64* expression and gain of *ins-17* expression. We also show that *mab-5* is required for the differential gene expression of the guanylyl cyclase *gcy-35* and the neuropeptide *flp-8* between AVM and PVM, the sisters of the SDQ neurons. Loss of *mab-5* results in the onset of *gcy-35* expression loss of *flp-8* expression in PVM. Lastly, we show that *mab-5* also regulates the differential expression of the neuropeptides *flp-20* and *nlp-66* between AQR and PQR. Together, these data suggest that Hox gene expression is both necessary and sufficient throughout life to establish neuronal diversity.

Disclosures: E. Child: None. **T. Barney:** None. **E. Davis:** None. **M. Lyman:** None. **S. Bennett:** None. **A. Rolfson:** None. **S.R. Taylor:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.03/D3

Topic: A.01. Neurogenesis and Gliogenesis

Title: Msx1 marks a distinct, multipotent, and self-renewing cerebellar rhombic lip population.

Authors: *M. KE[1], J. T. YEUNG[1], M. RAHIMI-BALAEI[2], E. CHEN[3], A. UDUMULLAGE[3], D. GOLDOWITZ[1];
[1]Med. Genet., [2]Human Anat. and Cell Sci., [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Understanding the processes of cell fate specification for neural progenitor cells is essential to the study of neurodevelopment and associated disorders. The cerebellum is an advantageous structure for studying cell fate specification of neurons given its small number of well characterized and organized neuron types, positioned in specific layers of the cerebellar cortex or within the cerebellar nuclei. The rhombic lip is the germinal zone that produces all Glutamatergic/excitatory neurons of the cerebellum, while the ventricular zone produces all GABAergic/inhibitory neurons of the cerebellum. Our lab has previously demonstrated the molecular compartmentalization of the embryonic rhombic lip into the Wls+/Atoh1- interior (iRL) and Wls-/Atoh1+ exterior face (eRL) of the rhombic lip. Recently, we also found that the transcription factor Msx1, a known downstream effector of BMP signaling and known to repress cell differentiation, is also expressed in the iRL. Therefore, we hypothesized that the iRL contains the reservoir of *Msx1*-expressing cells in the rhombic lip that replenish the Atoh1+ cells of the eRL as they migrate out, thereby regulating the production of each glutamatergic neuron type. We conducted a histological examination of the *Msx1*-KO mouse. An accumulation of granule neurons and depletion of unipolar brush cells was observed at embryonic day 18.5 in the *Msx1*-KO. At E13.5, a greater number of cells were observed migrating in the subpial stream in the Msx1-KO. Taken together, these results suggest that the earlier-born glutamatergic neuron types are being produced at the expense of the later-born unipolar brush cells. Next, we mapped the fate of *Msx1*-expressing progenitors of the cerebellum using a genetic inducible fate-mapping mouse model (Msx1-CreERT2/Ai14D) across embryonic time as well as postnatal timepoints. All three glutamatergic neuron types were labeled with tamoxifen injections at embryonic day 9.5 (E9.5) and examination at E13.5 and E18.5. Furthermore, labeling of Purkinje neurons was observed even though *Msx1* expression is absent from the ventricular zone. This suggests that the *Msx1*-expressing progenitors of the rhombic lip are still capable of acquiring GABAergic identity and thus may be the most stem-like of the rhombic lip cell populations. The distribution of Msx1 progenitor-derived Purkinje neurons across the adult cerebellum is currently being assessed. Overall, investigating the *Msx1* progenitors will uncover some of the fundamental mechanisms by which acquisition of Glutamatergic versus GABAergic cell fate occurs.

Disclosures: M. Ke: None. **J.T. Yeung:** None. **M. Rahimi-Balaei:** None. **E. Chen:** None. **A. Udumullage:** None. **D. Goldowitz:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.04/D4

Topic: A.01. Neurogenesis and Gliogenesis

Title: Characterization of Hedgehog pathway components in the developing and adult cortex

Authors: *D. HERNANDEZ;
Cell. and Developmental Biol., Univ. of Michigan, ann arbor, MI

Abstract: *Characterization of Hedgehog pathway components in the developing and adult cortex*
The neocortex is an integral component of cognitive function and sensory processing, including language, decision-making, and voluntary movements. The proper formation of this complex structure relies on the integration of multiple signaling pathways, including the Hedgehog (HH) pathway, a key regulator of neurogenesis. In the developing neocortex, Sonic HH (SHH) ligands bind to the canonical receptor, Patched (PTCH1), relieving its inhibition of the GPCR-like protein Smoothened (SMO). Activated SMO accumulates in the primary cilium and triggers a signal transduction cascade that regulates the activity of the Glioma-associated (GLI) family of transcription factors (GLI1-3), which drives HH pathway responses. HH signaling is essential for embryonic and postnatal development and is a key mitogen during corticogenesis, regulating progenitor maintenance and proliferation. In addition to its proliferative effects, within the central nervous system (CNS) HH signaling also regulates cell fate specification, axon guidance, cell migration, and cell survival. Loss-of-function HH pathway mouse mutants in the cortex display holoprosencephaly (failure of forebrain hemisphere division), while gain-of-function HH pathway mouse mutants exhibit exencephaly (brain develops outside the skull). ***Although HH signaling plays well-established roles in cortical development, the downstream GLI-dependent transcriptional mechanisms that drive corticogenesis remain poorly understood.*** To address this gap, I will initially investigate the spatial and temporal expression patterns of key HH pathway components, including *Shh*, *Gli1-3*, and *Ptch1* in the developing cortex. I will use *lacZ* reporter mice, along with in situ hybridization to visualize RNA expression in embryonic, postnatal, and adult brain tissue, combined with immunofluorescence to identify the specific cell types that express these transcripts. Through this, I expect to identify distinct and dynamic expression patterns of HH pathway components in the developing/adult cortex. Additionally, I will utilize a recently developed epitope-tagged *Gli* allele mouse model ($Gli1^{FLAG/FLAG};Gli2^{HA/HA};Gli3^{V5/V5}$, referred to as Gli^{FHV}) to visualize endogenous GLI proteins during embryonic and postnatal cortical development and throughout adulthood. I will also use these mice to identify GLI-dependent transcriptional targets. Future experiments will investigate the individual and combined functional contributions of *Gli1-3* through conditional deletion of these genes during mouse cortical development.

Disclosures: D. Hernandez: None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.05/D5

Topic: A.01. Neurogenesis and Gliogenesis

Title: Characterizing the effects of disrupting ganglionic eminence-specific chromatin interactions on interneuron development

Authors: *A. MARTIARTU[1], A. P. APPU[2], Y. ZHANG[2], T. J. PETROS[3];
[1]NICHD, NIH, Rockville, MD; [2]NICHD, NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Bethesda, MD; [3]Developmental Neurosci. Br., NICHD, Rockville, MD

Abstract: Normal brain function is dependent on a delicate balance between excitatory neurons and GABAergic interneurons (INs). The abnormal development, and thus dysfunction, of INs has been associated with various disorders, including schizophrenia, autism, and epilepsy. Most INs are born in the ganglionic eminences (GEs) during embryogenesis. The GEs are divided into three structures: the medial (MGE), lateral (LGE), and caudal ganglionic eminences (CGE), each giving rise to specific IN subtypes. There is evidence that epigenomic changes can modulate cell development; however, how these changes impact IN development remains largely unexplored. Here, we investigate the unique region-specific chromatin structure of Nkx2.1, a critical transcription factor for the development of MGE-derived INs. We utilize a novel strategy consisting of the genomic insertion of CTCF motifs to generate two mutant mouse lines with the aim of disrupting two unique chromatin interactions: an MGE-specific promoter-promoter chromatin interaction between Nkx2.1 and a neighboring gene MBIP, and a non-MGE specific promoter-repressor region interaction between Nkx2.1 and neighboring genes Nkx2.9 and Pax9. Our results indicate that the disruption of the Nkx2.1-MBIP interaction downregulates MBIP expression in the GEs with no effect on Nkx2.1 expression and the development of MGE-derived INs in the cortex. Micro-C reveals the CTCF insertions weakly disrupt the Nkx2.1-Nkx2.9 interaction, but do not influence the Nkx2.1-Pax9 interaction. In the future, we will characterize the effects of disrupting Nkx2.1-MBIP and Nkx2.1-Nkx2.9 interactions on the development of INs in the striatum, globus pallidus, olfactory bulbs and GABAergic projection neurons.

Disclosures: A. Martiartu: None. **A.P. Appu:** None. **Y. Zhang:** None. **T.J. Petros:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.06/D6

Topic: A.01. Neurogenesis and Gliogenesis

Title: Determining the role of regulated ubiquitin activation by UBA1 during neuronal cell-fate decisions

Authors: *F. SHAFIGHI[1,2], A. WERNER[1];
[1]Stem Cell Biochem. Section, Natl. Inst. of Dent. and Craniofacial Res., Bethesda, MD;
[2]Neurosci. and cognitive Sci. program, Univ. of Maryland Col. Park, College Park, MD

Abstract: Ubiquitylation is an essential post-translational modification that regulates many aspects of development and stem cell differentiation decision making. This process takes place as three distinct steps: activation, conjugation and ligation, performed by E1, E2 and E3 enzymes, respectively. Due to its key role in differentiation, this system must be dynamically regulated. Prior research has shown that regulation occurs at the level of E2-E3 or E3-substrate interaction. However, less is known if and how regulation at the beginning of the ubiquitylation process contributes to cellular differentiation and development. UBA1 is the major E1 enzyme in human cells and it is translated as two isoforms, nuclear UBA1a, initiated from M1, and cytoplasmic UBA1b, initiated from M41. Recently, we discovered that nuclear and cytoplasmic UBA1 are dynamically regulated during hematopoiesis and reduction in UBA1b through somatic variations in UBA1 at position M41 causes a myeloid differentiation bias. These observations demonstrated that subcellular regulation of E1 enzyme function and spatially controlled ubiquitin activation are essential for normal hematopoiesis. Yet, whether this type of regulation is required for other differentiation processes is unclear. Here, we show that the presence of cytoplasmic UBA1b is essential in fate determination and function of iPSC-derived cortical-like neurons. Differential expression of a UBA1 mRNA that predominantly promotes translation of UBA1b is crucial for proper differentiation process. Intriguingly, CRISPR-mediated reprogramming of this UBA1 mRNA to prevent UBA1b upregulation during neurogenesis causes differentiation defects. UBA1b deficiency in the cytoplasm during neuronal differentiation resulted in dysregulation of genes involved in several cellular processes including axonal growth, synaptic organization, and synaptic vesicle packaging. These morphological and functional changes could be confirmed by immunofluorescence analysis. Currently, we are using biochemical and proteomic approaches to determine how loss of cytoplasmic UBA1b leads to these phenotypes. Together, our results demonstrate that regulation of UBA1 subcellular localization and spatially controlled ubiquitin activation is a crucial mechanism in cell-fate determination during neuronal development.

Disclosures: F. Shafighi: None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.07/D7

Topic: A.01. Neurogenesis and Gliogenesis

Support: 1 R21 MH129995-01
1 T32NS115656-01A1

Title: A transcriptomic blueprint for the development and social behavioral programming of the sexually dimorphic mammalian Medial Amygdala

Authors: *A. ABU IRQEBA[1], A. ABBONDANZA[3], S. KUMAR[4], N. PRAKASH[5], G. WALKER[6], S. FELSEN[7], J. E. LISCHINSKY[8], D. LIN[9], K. HSIAO[2], Z. LI[10], T. F. HAYDAR[11], J. CORBIN[12];
[1]Children's Natl. Med. Ctr., Washington, DC; [2]Children's Natl. Med. Ctr., washington, DC; [3]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC; [4]Children's Natl., Washington DC, DC; [5]Children's Natl. Hosp., Washington, DC; [6]Howard Univ., Washington, PA; [7]George Washington Univ. Integrated Biomed. Sci., Washington, DC; [8]Neurobio., Natl. Inst. of Envrn. Hlth. Sciences/NIH, Durham, NC; [9]Neurosci. Inst., New York Univ. Sch. of Med., New York, NY; [10]Boston Univ., Boston, MA; [11]Anat. and Neurobio., Boston Univ. Chobanian and Avedisian Sch. of Med., Boston, MA; [12]Childrens Natl. Hosp., Washington, DC

Abstract: The social brain network (SBN) is comprised of a group of structures that process sensory cues to drive a host of learned and unlearned social behaviors. The medial amygdala (MeA) is a sexually dimorphic forebrain SBN structure that processes olfactory cues and drives social behaviors, including aggression, mating, and predator avoidance. Many of these social behaviors are necessary for survival, but how they arise is not well understood. To unravel the transcriptional underpinnings of MeA sexually dimorphic formation and how these processes preconfigure circuits for later emerging behaviors, we conducted developmental snRNA-seq analysis that followed MeA neurons across their maturation including during embryonic birth, migration, and pre-pubertal circuit formation. We found that the pre-pubertal MeA is comprised of 24 GABAergic and 40 Glutamatergic neuronal subtypes, arising from complex and spatially distinct progenitor sources within the embryonic brain, including the telencephalon and diencephalon. We reveal distinct timing and patterns for their origin and uncover the transcriptomic complexity required for the maturation of inhibitory and excitatory neurons destined for the MeA. We further identify a divergence in transcriptional identity for MeA neurons emerging during embryogenesis and find that mature transcriptional signatures are detectable by birth indicating early establishment of neuronal identity. Using in vivo fiber photometry, we additionally demonstrate that early developmental programming of excitatory neurons preconfigures later function in select social behavioral processes, thus tying origin and programming to later function. Together, for the first time, our study outlines a comprehensive transcriptomic blueprint for the sexually dimorphic timing, origin, and specification of the diverse neuronal populations that comprise the MeA and their roles in adult social behaviors.

Disclosures: A. Abu Irqeba: None. **A. Abbondanza:** None. **S. Kumar:** None. **N. Prakash:** None. **G. Walker:** None. **S. Felsen:** None. **J.E. Lischinsky:** None. **D. Lin:** None. **K. Hsiao:** None. **Z. Li:** None. **T.F. Haydar:** None. **J. Corbin:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.08/D8

Topic: A.01. Neurogenesis and Gliogenesis

Support: DP2MH132940
R01MH133181
U01NS132161
ZIAMH002984

Title: Conserved transcriptomic gradients organise thalamocortical projections in mouse and marmoset

Authors: ***A. Y. FAN**[1,2], J. SCOTT[1], N. M. KUEHN[1], M. MAJEED[3], H. QI[4], M. T. SUMMERS[3], J. V. CHANDRASHEKAR[3], H. ZHAN[5], J. M. KEBSCHULL[4], X. CHEN[3], J. A. BOURNE[1];
[1]NIMH, Bethesda, MD; [2]Monash Univ., Clayton, Australia; [3]Allen Inst., Seattle, WA; [4]Johns Hopkins Univ., Baltimore, MD; [5]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: The thalamus is reciprocally connected with the entire cortex and is its principal source of extracortical input. How the precise wiring between the thalamus and cortex is established during development, leading to differences in mature circuits across species, is unknown. Understanding the rules governing thalamocortical wiring is particularly critical in primates, in which the cortex and thalamus have each undergone independent expansion and diversification. To begin to address how these wiring rules arise, we first asked how they are organised in the mature brain. Here, we investigated the organisation of thalamocortical projections by integrating spatial transcriptomics with barcoded connectomics in the higher-order sensory thalamus of the marmoset and mouse, profiling gene expression in 1.5 million neurons across marmoset hemibrain sections and jointly mapping the projections and transcriptomic identities of 708 marmoset and 1,518 mouse neurons. In contrast to the classical view of discrete thalamic nuclei, gene expression and thalamocortical projections varied as continuous gradients that crossed nuclear boundaries, and these expression gradients aligned with the anterior-posterior topography of thalamocortical projections. This gene-to-projection correspondence was conserved between mouse and marmoset despite extensive reorganisation of both structures. We speculate that this conserved gene gradient is a remnant of a developmental axis that establishes early thalamocortical topography. Ongoing work in developing brains will test whether a similar gene-projection topographical relationship is preserved across early life.

Disclosures: A.Y. Fan: None. **J. Scott:** None. **N.M. Kuehn:** None. **M. Majeed:** None. **H. Qi:** None. **M.T. Summers:** None. **J.V. Chandrashekar:** None. **H. Zhan:** None. **J.M. Kebschull:** None. **X. Chen:** None. **J.A. Bourne:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.09/D9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Notch signaling promotes the generation of retinal ganglion cells in human retinal organoids

Authors: *R. FREUND, B. GUY, R. JOHNSTON;
Biol., Johns Hopkins Univ., Baltimore, MD

Abstract: Retinal ganglion cells (RGCs) are long projection neurons that transmit light information from the retina to the brain. RGCs cannot be regenerated after early development, and their death underlies irreversible blinding conditions like glaucoma. The lack of accessible and experimentally tractable human retinal tissue has made studies of developing human RGCs challenging. Human retinal organoids provide a powerful model to overcome this, as they recapitulate the cytoarchitecture and developmental timing of the human retina in vitro. In the developing retina, the Notch signaling pathway is a critical regulator of progenitor cell pool maintenance and differentiation. At early stages of organoid development, Notch inhibition causes retinal progenitor cells (RPCs) to differentiate into photoreceptors at the expense of other fates, most notably RGCs. To test the hypothesis that active Notch signaling promotes RGC fate, we treated organoids with the Notch ligand Delta (DLL1) or the inhibitor DAPT. DLL1 extended the temporal window of RGC generation, increased the size of the ganglion cell layer (GCL), and increased RGC density within the GCL. This increase occurred while the RPC pool was maintained, suggesting that DLL1 promotes proliferation and biases differentiation toward RGC fate. Conversely, DAPT treatment decreased RGC density and, during certain temporal windows, caused widespread RGC death. Together, our results suggest that Notch signaling promotes RGC generation, thereby establishing a framework to engineer RGC-enriched retinal organoids for therapeutic applications.

Disclosures: R. Freund: None. **B. Guy:** None. **R. Johnston:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.10/D10

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant EY031403
Maine INBRE

Title: Developmental transcription factors induce generation of functional retinal ganglion cells by postnatal progenitors

Authors: *L. COSTEA[1,2], R. MEZILE[3,2], M. ZAYD[2,3], B. K. YOUNG[4], J. L. GOLDBERG[5], L. C. GREIG[3], M. B. WOODWORTH[2];
[1]Harvard (SCRB, CBS), Cambridge, MA; [2]Neurosci., Bates Col., Lewiston, ME; [3]Ophthalmology, UCSF, San Francisco, CA; [4]Ophthalmology and Visual Sci., [5]Byers Eye Institute--Ophthalmology, Stanford Univ., Palo Alto, CA

Abstract: To repair the damaged central nervous system, it is crucial to understand regulation of neuronal differentiation from endogenous progenitors. Progenitors of the developing mammalian retina first produce early-born neurons, including retinal ganglion cells (RGCs), then cease production of RGCs as they produce later-born neurons and glia. Here, we identify a set of developmentally expressed transcription factors TFs that enables late retinal progenitors to revert to earlier patterns, generating RGCs outside their normal developmental window before returning to produce later-born cells. Despite being born one week later than their endogenous counterparts, these induced RGCs migrate to appropriate locations, acquire mature morphologies, express appropriate genes closely matched to endogenous RGCs, establish synaptic contacts, respond to light stimulation, and extend axons that reach visual targets in the brain. Taken together, these results indicate that developmental transcription factors can prompt late retinal progenitors to generate functional RGCs, providing proof of principle for regenerative approaches in the mammalian retina.

Disclosures: L. Costea: None. **R. Mezile:** None. **M. Zayd:** None. **B.K. Young:** None. **J.L. Goldberg:** None. **L.C. Greig:** None. **M.B. Woodworth:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.11/D11

Topic: A.01. Neurogenesis and Gliogenesis

Support: Retinal Research Foundation
Research Preventing Blindness
DoD Vision program
McKnight Foundation

Title: Insm1-mediated regulation of retinal development and regeneration

Authors: *T. HOANG;
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Abstract: The transcription factor Insulinoma-associated 1 (Insm1) is expressed during neurogenesis in multiple regions of the nervous system, but its role in retinal development and regeneration remains poorly defined. We combined genetic, molecular, and functional approaches to determine the role of Insm1 in retinal neuron production and Müller glia reprogramming.Insm1 expression is enriched in neurogenic retinal progenitors and immature neurons in both mouse and human retinas. Our lineage tracing revealed that Insm1-expressing progenitors generate all major retinal neuronal classes and Müller glia. Conditional deletion of Insm1 in retinal progenitors resulted in significant reductions in retinal thickness, overall cell number, and neuronal populations marked by OTX2 and HuC/D, accompanied by Müller glia activation and progressive visual dysfunction. TUNEL analysis detected no significant increase in apoptosis during early developmental stages, suggesting that impaired neuronal production rather than cell death underlies the phenotype. Conversely, inducible Insm1 overexpression promoted neuronal differentiation and suppressed Müller glia formation during retinal development.To examine the reprogramming potential of Insm1, we generated a Müller glia-specific inducible Insm1 overexpression mouse model. Following NMDA-induced retinal injury, Insm1 expression alone induced limited Müller glia-to-neuron conversion. Pharmacological inhibition of HDACs, EZH2, H3K9 methyltransferases, or Notch signaling significantly enhanced neuronal production. Furthermore, combined Insm1 overexpression and Müller glia-specific deletion of the Notch mediator Rbpj induced robust neuronal regeneration. Regenerated cells expressed markers of bipolar (ISL1, SCGN), amacrine/horizontal (TFAP2A), and cone photoreceptor (ARR3) lineages. Patch-clamp recordings demonstrated that regenerated bipolar-like and amacrine-like neurons exhibited light-evoked responses and neuronal membrane properties distinct from Müller glia.Together, these findings identify Insm1 as a central regulator of retinal neurogenesis and reveal its ability to activate latent regenerative programs in adult Müller glia, particularly when combined with removal of Notch-mediated repression.

Disclosures: T. Hoang: None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.12/D12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NEI Grant S10OD28612
NEI Grant P30EY007003
NIH Grant P40OD011021

Title: Injury context and retinoic acid signaling regulate cell fate determination during zebrafish retinal regeneration

Authors: *L. RAPPAPORT DA COSTA SANTOS[1], M. NAGASHIMA[1], P. F. HITCHCOCK[1], T. HOANG[2];
[1]Dept. of Ophthalmology and Visual Sci., Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Ophthalmology and Visual Sci., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Müller glia in the zebrafish retina possess the remarkable ability to regenerate neurons following injury; however, it remains unclear whether regenerated neurons fully recapitulate the diversity of endogenous cell types and how their fate is controlled. In this study, we used an inducible genetic lineage-tracing system that permanently labels reprogrammed Müller glia and their progeny. To determine how injury context and developmental signaling pathways influence neuronal diversity and fate specification during retinal regeneration, we compared regenerative outcomes across two distinct lesion paradigms, photoreceptor-selective light damage and NMDA-induced inner retinal injury, and under conditions where developmental signaling was pharmacologically altered.
Immunohistochemistry using cell type-specific markers demonstrated that for both injury paradigms Müller glia regenerate all major retinal neuron classes, confirming broad regenerative competence. However, quantification of regenerated cone photoreceptors and retinal ganglion cells revealed significant difference in neuronal proportions between light-damaged and NMDA-injured retinas, suggesting that the injury context influences regenerative outcomes.
Because proper retinal function relies on subtype-level diversity, we further examined subtypes of regenerated amacrine cells, one of the most heterogeneous populations in the retina. Immunohistochemistry against neurotransmitter markers revealed that both injury models successfully regenerated GABAergic, cholinergic, and dopaminergic amacrine cell subtypes. Furthermore, morphological analysis showed that regenerated cholinergic amacrine cells exhibited the precise dendritic stratification patterns characteristic of starburst amacrine cells, demonstrating the restoration of neurochemical and morphological features.
Finally, we determined whether manipulating developmental cell-fate pathways, specifically retinoic acid (RA) signaling and thyroid hormone (T3), could bias the fate of regenerated neurons. Treatment with the RA signaling inhibitor BMS-493 following light damage significantly impaired regeneration of cone photoreceptors, suggesting that RA signaling is required for photoreceptor differentiation during regeneration. Conversely, treatment with T3 following NMDA injury did not significantly alter the proportions of neuronal populations. Together, these findings show that MG-mediated regeneration recapitulates the endogenous neuronal diversity, including amacrine cell subtypes, while injury context and RA signaling can influence the fates of regenerated neurons.

Disclosures: L. Rappaport da Costa Santos: None. **M. Nagashima:** None. **P.F. Hitchcock:** None. **T. Hoang:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.13/D13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NJGCA Grant CAUT26GFP004

Title: Prenatal Interleukin-6 Exposure alters gene expression in neural progenitors

Authors: *R. ZARITSKY[1], F. JANCZUR VELLOSO[2], S. W. LEVISON[3];
[1]Rutgers Unversity, Newark, NJ; [3]Pharmacology, Physiol. & Neurosci., [2]Rutgers Univ., Newark, NJ

Abstract: The incidence of Autism Spectrum Disorder (ASD) is rising, highlighting the importance of studying the influence of contributing environmental factors. Maternal immune activation, particularly involving elevated levels of the pro-inflammatory cytokine IL-6, which is able to cross into the fetal brain, has been consistently linked to increased ASD risk in the offspring. Our group has developed a novel mouse model to show that transiently increasing early postnatal levels of IL-6 leads to behavioral abnormalities associated with ASD, including impaired sociability, altered communication, and increased repetitive behavior. Notably, these effects occur without induction of neuroinflammation or microglial activation, isolating direct effects of IL-6 on neurodevelopment. However, the mechanisms by which IL-6 impacts brain development are poorly understood. Our lab has hypothesized that IL-6 disrupts neurogenesis and gliogenesis by altering gene expression of neural progenitors (NPs) arising from the subventricular zone (SVZ) during the gestational period. These NPs will later produce interneurons, astrocytes, and oligodendrocytes that populate the neocortex. We have previously identified 8 sub-populations of NPs using antigenic profiles and have demonstrated heterogeneity in responses to IL-6, with one subpopulation proliferating more while all others proliferate less. In this study, we have built on our previous characterization of neural progenitors by using a novel combination of Parse Biosciences Split-Seq and CITE-Seq technologies to analyze the impact of our IL-6 administration paradigm on gene expression in neural progenitor populations. Using this method, we have identified 21 unique cell populations. We have identified Cdk8, a key regulator of stem cells, as being significantly upregulated in mouse SVZ cells following IL-6 administration and have found increases in genes related to transcriptional regulation and decreases in genes related to mitochondrial energy synthesis with IL-6 administration.

Disclosures: R. Zaritsky: None. **F. Janczur Velloso:** None. **S.W. Levison:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.14/D14

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant EY031403
Maine INBRE

Title: Transcriptional Controls Over the Development of Retinal Ganglion Cells in the Mouse

Authors: *N. A. ROSSILLI, M. B. WOODWORTH, T. HOLLAND, N. DELAMATER; Neurosci., Bates Col., Lewiston, ME

Abstract: Retinal ganglion cells (RGCs) are neurons that function critically in transmitting processed visual information from the retina to the brain. Death or injury to RGCs results in irreversible vision loss, as the adult mammalian retina cannot regenerate or repair itself. Many transcription factors are known to influence the fate of early-born neurons as they are produced by retinal progenitors and develop RGC identity, but further transcriptional controls remain to be identified. In previous work in our laboratory, we identified a proneural transcription factor (TF) of the zinc finger superfamily as one of a group of factors that can induce the generation of ectopic RGCs from late-stage progenitors in the mouse retina and hypothesized that this TF, when expressed by retinal progenitor cells, may promote RGC identity. We find that this TF is expressed by RGCs starting at early postnatal ages and persisting through adulthood. In this work, we investigate TF function in the development of RGC identity and connectivity by both loss- and gain-of-function approaches in mice in vivo. Overall, we aim to understand genetic controls over RGC development, which can contribute to efforts to regenerate RGCs and restore vision.

Disclosures: N.A. Rossilli: None. **M.B. Woodworth:** None. **T. Holland:** None. **N. Delamater:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.15/D15

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant EY031403
Maine INBRE

Title: Effects of Gap43 on Retinal Ganglion Cell Axon Guidance

Authors: *M. HAJDUK[1], C. ZIEHL[1], R. GLASER[1], N. DELAMATER[1], M. B. WOODWORTH[2];
[2]Neurosci., [1]Bates Col., Lewiston, ME

Abstract: Retinal ganglion cells (RGCs) are neurons in the retina that send axon projections through the optic nerve, relaying stimuli to the visual processing cortex of the brain. Upon injury,

mammalian RGCs cannot be regenerated, leading to irreparable vision loss. In prior work, we have identified genetic controls that induce RGCs to differentiate from late-stage retinal progenitor cells. These induced RGCs express the canonical growth-cone-associated gene gap43 at exceptionally high levels compared with control neurons. We aim to understand the function of gap43 in induced RGC axonal pathfinding in vivo. To investigate this, we use a mouse model where RGCs are induced from late-stage progenitors in postnatal animals and manipulate Gap43 expression via plasmid-based overexpression or knockdown. Employing overexpression constructs to upregulate the expression of gap43 in induced RGCs, or CasRx-based knockdown to reduce expression, allows us to study differences in axon outgrowth patterns, pathfinding efficacy, and number of projected axons as compared with control induced RGCs. Through investigation of gap43 upregulation and knockdown, we hope to better understand its function and significance in axonal pathfinding, gaining information that may aid in the work of healing vision damage and loss in humans.

Disclosures: M. Hajduk: None. **C. Ziehl:** None. **R. Glaser:** None. **N. Delamater:** None. **M.B. Woodworth:** None.

Poster

PSTR209: Transcriptional Control of Neural Cell Fate, Progenitor Specification, Circuit Formation, and Regeneration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR209.16/D16

Topic: A.01. Neurogenesis and Gliogenesis

Support: Intramural Research program of the National Institutes of Health (1ZIAMH002881 to Zheng Li)

Title: Drp1 S616 Phosphorylation Is Enriched in Parvalbumin Interneurons and Regulates Hippocampal PV Neuron Abundance

Authors: *R. TIAN[1,2], R. FUSHA[1,2], Z. LI[1,2];
[1]NIH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Mitochondrial fission is essential for neuronal function, contributing to ATP production, calcium buffering, and mitochondrial quality control. Phosphorylation of dynamin-related protein 1 (Drp1) at serine 616 promotes mitochondrial fission and is tightly regulated to support neural circuit development and synaptic function. However, whether Drp1 S616 phosphorylation exhibits subtype-specific regulation across neuronal populations remains unknown. To examine cell type-specific Drp1 S616 phosphorylation, we performed phospho-Drp1(S616) immunostaining in the somatosensory cortex and hippocampus of adult Thy1-GFP-M mice, in which sparse pyramidal neurons express EGFP, together with immunolabeling for parvalbumin (PV) and somatostatin (SST) interneurons. PV interneurons exhibited the highest phospho-Drp1 levels among all neuronal populations examined. In both the somatosensory

cortex and hippocampus, PV interneurons displayed significantly higher phospho-Drp1 levels than pyramidal neurons. SST interneurons also exhibited elevated phosphorylation compared with pyramidal neurons. To assess the functional significance of Drp1 S616 phosphorylation in PV neurons, we analyzed phosphorylation-deficient Drp1 S616A mutant mice. Notably, Drp1 S616A mice exhibited reduced hippocampal PV neuron abundance relative to control littermates. These findings identify PV interneurons as a neuronal population with exceptionally elevated Drp1 S616 phosphorylation and suggest that phosphorylation-dependent mitochondrial dynamics contribute to the maintenance of normal hippocampal PV neuron abundance. The pronounced enrichment of Drp1 S616 phosphorylation in PV interneurons identifies a previously unrecognized molecular signature of this neuronal subtype.

Disclosures: R. Tian: None. **R. Fusha:** None. **Z. Li:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.01/D17

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI: JP23K23894
JSPS KAKENHI: JP25K02283

Title: How cerebellar neural progenitors generate diverse neurons

Authors: *H. ZHANG[1], Y. KOYAMA-FUJII[2], J. WANG[3], T. SHIMIZU[2], M. HIBI[2];
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Abstract: The cerebellum is essential for motor coordination and learning and is also implicated in higher cognitive functions. Its function depends on neural circuits conserved across vertebrates. These circuits comprise multiple neuronal types. In zebrafish, granule cells (GCs) are the principal glutamatergic excitatory neurons. They receive inputs and project parallel fibers to the dendrites of Purkinje cells (PCs). PCs are GABAergic neurons that also receive climbing fiber input from inferior olivary (IO) nuclei, integrate these signals, and relay cerebellar output via eurydendroid cells.
In zebrafish, PCs and GABAergic interneurons are thought to derive from ptf1a-expressing progenitors in the ventricular zone, whereas glutamatergic GCs arise from atoh1a/b/c-expressing progenitors in the upper rhombic lip. However, recent studies suggest that ptf1a+ progenitors may also generate a GC subpopulation, highlighting their broader developmental potential. In addition, ptf1a+ progenitors in the posterior hindbrain give rise to glutamatergic IO neurons. Meanwhile, although PCs are often considered uniform, emerging evidence indicates functional and morphological diversity. The mechanisms underlying differentiation of these neuronal types

from ptf1a+ progenitors remain unclear.
To address this, we generated a single-cell transcriptomic dataset of ptf1a+ lineage cells and PCs using FACS in transgenic zebrafish. We confirmed that ptf1a+ progenitors generate multiple neuronal types, including PCs, GABAergic interneurons, IO neurons, and GCs. We also identified an atoh1a/b/c+ progenitor population and trajectory evidence suggesting that GCs can arise from ptf1a+ progenitors through an atoh1c-expressing intermediate state. Importantly, we established a transcriptional atlas of zebrafish PCs and defined molecularly distinct PC subpopulations. We identified subtype-enriched marker genes for each population and validated several of these markers by in situ hybridization. Spatially restricted expression patterns revealed that individual markers label discrete PC subsets within specific cerebellar regions, demonstrating previously unappreciated molecular and anatomical heterogeneity among zebrafish PCs. Together, these findings established a comprehensive single-cell atlas of ptf1a-derived cerebellar lineages, defined molecularly distinct PC subpopulations and their markers, and provided a framework for understanding how cerebellar neural progenitors generated diverse neuronal lineages in the zebrafish cerebellum.

Disclosures: H. Zhang: None. **Y. Koyama-Fujii:** None. **J. Wang:** None. **T. Shimizu:** None. **M. Hibi:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.02/D18

Topic: A.01. Neurogenesis and Gliogenesis

Support: IFER Graduate Fellowship

Title: Subplate neurons as a model of input dependent human neuronal maturation

Authors: *N. SELE[1,2], F. BIREY[2,3];
[1]Emory Univ. Neurosci. Grad. Program, Atlanta, GA; [2]Dept. of Human Genet., [3]Dept. of Pediatrics, Emory Univ., Atlanta, GA

Abstract: Developmental maturation of human neurons underlies a series of highly inter-connected and evolutionarily divergent set of processes which are critical in endowing them with functionally relevant physiological properties. However, due to its highly specialized nature in humans, animal models are limited in their ability to accurately represent the mechanisms behind this process. Here, we propose to leverage in vitro and ex vivo human subplate cells, which is a group of anachronistically mature neurons that populate the transient subplate region of the fetal cortex, as a model to study the molecular and cellular mechanisms underlying human neuronal maturation. Subplate neurons are among the first targets of thalamocortical innervations that emerge during mid gestation and are thought to drive subplate development, rendering it a uniquely well-suited model of investigating cell-intrinsic and cell-extrinsic aspects of its

developmental maturation. Towards this, first, we establish the presence of subplate-like cells in human cortical organoids (hCO) using RNA-sequencing and immunofluorescence to confirm the presence of cells that express markers enhanced in the subplate. Then, we employ a novel tripartite thalamocortical assembloid model by fusing cortical, subpallial (human subpallial organoids; hSO) and diencephalic organoids (hDiO) in order to replicate interregional connections that provide extrinsic cues to aid in the maturation of subplate cells. We show that neurons from hDiO extend axons through the hSO to hCO, and through the use of anterograde transsynaptic tracing, we confirm that these thalamocortical fibers create functional synapses with cells in the hCO. Then, we utilize an optogenetic stimulation paradigm along with calcium imaging to display that thalamocortical input is able to modulate the frequency and amplitude of calcium transients in hCO neurons in an age-dependent manner. Finally, we perform single cell RNA-sequencing on hCOs from these groups and focus on subplate-like cells in these organoids to display that optogenetic stimulation upregulates several developmental and signaling cascade pathways, related to a more mature state in subplate-like cells that receive thalamocortical input. Through these results, we display our model's ability to replicate an environment that is close to the *in vivo* subplate, as well as the contribution of thalamocortical inputs to push subplate-like cells to a more mature state, demonstrating a mechanism through which extrinsic factors contribute to human neuronal maturation.

Disclosures: N. Sele: None. **F. Birey:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.03/D19

Topic: A.01. Neurogenesis and Gliogenesis

Support: 4K00NS129170-03

Title: Activity dependent transcriptional and functional maturation of human MGE derived GABAergic lineages

Authors: *E. L. CRESPO[1], S. PARVEEN[2], J. M. PARENT[1];
[1]Neurol., [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Forebrain inhibitory interneurons are among the most diverse neuronal populations in the mammalian brain, exhibiting significant heterogeneity in molecular identity, developmental origin, electrophysiological properties, and circuit function. To date, intracellular and intercellular signaling mechanisms underlying interneuron fate specification have been well characterized. Yet neurons are uniquely defined by their ability to generate and respond to electrical activity, which influences interneuron migration, maturation, and circuit integration during brain development. Building on studies in animal models, a progressive specification model posits that neural activity shapes the emergence of interneuron identity. Neural activity

and activity-dependent molecular signaling have been increasingly implicated in the maturation and diversification of medial ganglionic eminence (MGE)-derived interneurons, including parvalbumin (PV)-lineage populations. However, human MGE-derived PV interneurons have proven difficult to robustly generate and study in vitro, limiting investigation of activity-dependent mechanisms during human interneuron development.
Here, we use self-organizing single-rosette MGE organoids (MGEOs) and assembloids to define transcriptional and functional trajectories underlying human MGE-lineage maturation. We generated a developmental single-cell atlas of MGE-lineage maturation and benchmark emerging cortical and subpallial GABAergic populations against recently published organoid protocols and human fetal reference datasets, revealing activity-dependent states accompanying interneuron development and subtype emergence. Using a PV reporter line, we validate transcriptomic evidence of robust PV-lineage interneuron generation, including basket and chandelier cell populations. Cell type-specific viral enhancers were used to target GCaMP6 and Channelrhodopsin-2 (ChR2) to emerging PV populations, enabling longitudinal tracking of PV-lineage maturation and integration into dorsal forebrain assembloids. Multielectrode array recordings and optogenetic perturbations revealed putative fast-spiking interneurons and their cell-type contribution to emergent network activity and oscillatory dynamics. Together, our findings support a human model of progressive interneuron specification in which activity-dependent transcriptional states are linked to the functional maturation and subtype diversification of MGE-derived interneurons.

Disclosures: E.L. Crespo: None. **S. Parveen:** None. **J.M. Parent:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.04/D20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 1R15HD114135-01 to MSS

Title: Decoding Calcium Activity in Early Neural Development with Wavelet Analysis

Authors: *C. BARE[1], S. PAUDEL[2], M. S. SAHA[3];
[1]William & Mary, Williamsburg, VA; [2]Applied Sci., [3]Biol., Col. of William and Mary, Williamsburg, VA

Abstract: Calcium signaling is a key regulator of neural induction, patterning, and earlyexcitability, yet the fine-scale temporal structure of calcium activity during neurulation remains poorly understood in contrast to adult neuron activity. To determine how individual neural plate cells encode developmental information at this stage, we developed a continuous wavelet transform (CWT)-based pipeline to complement traditional peak detection methods that extracts multiscale temporal features from high-speed calcium imaging of Xenopus laevis

embryos at early neurula stages, when neuroepithelial identity is being established and cells begin diverging toward distinct fates. The framework quantifies dominant frequency, spectral bandwidth, band-limited power, and inter-event interval variability for thousands of single cells. Analysis of >2,000 neural plate cells in early neurula embryos using the genetically encoded calcium indicator GCaMP revealed multiple excitability phenotypes rather than a uniform field of activity. Peak event frequencies spanned more than an order of magnitude (~0.01-0.13 Hz), and band-limited power varied across six orders of magnitude. Inter-event interval variability (CV_{ISI}) ranged from near-zero to >1.4, distinguishing highly regular oscillators from irregular spikers and burst-like activity patterns. These features delineated distinct temporal classes: regular narrowband oscillators, broadband irregular spikers, high-power burst-prone cells, and near-silent ROIs. Although visually similar in raw traces, these classes differ in timing statistics that are known to selectively activate downstream pathways such as CaMKII, CREB, calcineurin, and NFAT. The temporal phenotypes likely reflect underlying developmental states—ranging from progenitors with variable responsiveness to inductive cues, to mechanically active cells experiencing morphogenetic strain, to early differentiating neurons exhibiting stabilized oscillatory calcium entry. Because calcium dynamics influence gene expression, cytoskeletal remodeling, and responsiveness to embryonicdevelopment signals, these classes provide insight into how neural plate cells may differentially interpret patterning cues and commit to distinct fates. By linking phenotypes to potential developmental roles, wavelet analysis at the single-cell level offers a foundation for connecting excitability states to fate specification, tissue mechanics, and environmental sensitivity across neurulation.

Disclosures: C. Bare: None. **S. Paudel:** None. **M.S. Saha:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.05/D21

Topic: A.01. Neurogenesis and Gliogenesis

Title: The role of Citron Kinase in cytokinesis of tyrosine hydroxylase neurons in the rat brain

Authors: J. POPP[1], N. MURTHY[2], R. F. STOUT, Jr.[3], *R. L. RAMOS[4];
[1]NYIT Col. of Osteo. Med., Westbury, NY; [2]New York Inst. of Technol. Col. of Osteo. Med., Sharon, MA; [3]New York Inst. of Technol. Col. of Osteo. Med., Centerport, NY; [4]New York Inst. of Technol. Col. of Osteo. Med., Old Westbury, NY

Abstract: Microcephaly in humans and rodent models is caused by mutation of genes important in cytokinesis such as *CIT.* In additional to reduced brain size, mutations in *CIT* lead to failed cytokinesis and the presence of binucleate neurons. The extent to which progenitors for different cell types require *CIT* remains unknown. One approach toward this gap in our understanding is to phenotype binucleate cells based on cell-type specific gene/protein expression. In the present study, we use immunohistochemistry against tyrosine hydroxylase (TH) as a tool to label specific

neuronal populations throughout the brain of the Flathead rat. This model has a spontaneous *Cit* mutation causing microcephaly, binucleate cells in the brain, and early lethality. We indeed find binucleate TH-expressing cells throughout the brain. These data indicate that the progenitors for TH-expressing cells such as dopaminergic neurons of the substantia nigra require *Cit* for cytokinesis.

Disclosures: J. Popp: None. **N. Murthy:** None. **R.F. Stout:** None. **R.L. Ramos:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.06/D22

Topic: A.01. Neurogenesis and Gliogenesis

Support: the Région Normandie through the NanoCellConnection-Chaire d'Excellence programme
the National Institute for Physiological Sciences, Japan.

Title: Functional and morphological formation of tiny connections in subarachnoid spaces in early postnatal mice revealed by time-lapse observation of advanced microscopy and 3D mapping of leptomeningeal cells of serial block-face scanning electron microscopy

Authors: *H. KOMURO[1,2,3], A. DEBONNE[2,3], M. BÉNARD[2,3], D. SCHAPMAN[2,3], S. LOOPRASERTKUL[4], C. CHAMOT[2,3], S. BERNARD[2], A. ARABO[2,3], N. OHNO[5,4], L. GALAS[2,3];
[1]Univ. de Rouen Normandie, Shaker Heights, OH; [2]Univ. de Rouen Normandie, Rouen, France; [3]PRIMACEN, Rouen, France; [4]Natl. Inst. for Physiological Sci., Okazaki, Japan; [5]Dept. of Anatomy, Div. of Histology and Cell Biol., Jichi Med. Univ., Shimotsuke, Japan

Abstract: Mammalian brains are covered by the leptomeninges, which consist of the pia mater (PM) and arachnoid mater (AM), and bathed in cerebrospinal fluid (CSF) in the subarachnoid space (SAS). In the SAS, subarachnoid trabeculae (SATs) anchor brains to the AM and stabilize positions during head movement. To date, SAT formation during development and after brain injury remains to be determined, because their tiny and fragile structures obstacle the study. Anatomically and molecularly distinct cell types are found in the leptomeninges, but intercellular interactions between these cells also are poorly understood. In this study, we examined (1) SAT behavior in live tissues using advanced microscopy and (2) nano-scale connections between leptomeningeal cells by taking a series of EM photos. In both studies, early postnatal (P1-P10) CD-1 mice (both sexes) were used. For live cell imaging, brains with leptomeninges were sectioned at 200 μm-thickness. Slices were stained with DiI (5 μg/ml), and placed in a micro-incubation chamber attached to the stage of a Leica microscope (STELLARIS 8). The use of an x93 glycerol immersion objective and an additional digital zoom factor allowed the visualization of SATs in the SAS. Time-lapse images were taken every 1-5 seconds for up to 2 hours. Several

characteristic features of SATs were found as follows. (a) SATs were not immovable structures, but laterally shifted their position on both arachnoid fibroblasts and pial fibroblasts. (2) Sizes (diameter) of SATs reversibly changed from thick to thin and vice versa. (3) Neighboring SATs could fuse and result in a single SAT. (4) SATs could retract and lose connection to other fibroblast-like cells. For 3D analysis of cell connections, mice were perfused with 2.5% glutaraldehyde and 4% paraformaldehyde. Cerebella with leptomeninges were dissected out, stained with heavy metals, and embedded in resin. To obtain a series of EM photos, we used serial block-face scanning electron microscopy (Gatan 3view/Zeiss ΣIGMA/VP & MARLIN) and array tomography SEM system (Zeiss ATLAS5). Serial images sequences were generated at 50 nm steps, providing image stacks >37 μm deep and 33x33 μm wide at a resolution of 5.5 nm per pixel. Serial EM images were processed, measured with ImageJ using FIJI plugins. Pia fibroblasts extended many tiny processes (50-300 nm in diameter) in three different directions (upward, downward, and laterally), and form nano-scale connections with arachnoid fibroblasts in AM, macrophages in SAS, microglia in SPS, and neighboring pial fibroblasts in PM, suggesting that leptomeningeal cells may interact with each other by means of nano-scale connections during early development.

Disclosures: H. Komuro: None. **A. Debonne:** None. **M. Bénard:** None. **D. Schapman:** None. **S. Looprasertkul:** None. **C. Chamot:** None. **S. Bernard:** None. **A. Arabo:** None. **N. Ohno:** None. **L. Galas:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.07/D23

Topic: A.01. Neurogenesis and Gliogenesis

Support: WPLab Inc.

Title: Evidence of neural damage following neonatal rat acetaminophen administration

Authors: *A. C. DUNGAN[1], J. W. VANRYZIN[2], M. DEVALAPALLI[3], J. FAGAN[3], W. PARKER[4], K. J. REISSNER[5];
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Abstract: Acetaminophen (APAP) is the most commonly used over-the-counter analgesic during perinatal periods. During APAP metabolism, some amount of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) is produced, which is largely neutralized by glutathione. As glutathione stores are depleted, less NAPQI is neutralized, leading to the formation APAP-protein adducts and subsequent cell death. In adults, this toxicity is evident in the liver and represents the primary mechanism of APAP overdose toxicity. However, the pathways

responsible for APAP metabolism are not fully developed in the neonatal liver, and accordingly the developing brain may be susceptible to APAP metabolic toxicity. To investigate the generation of APAP-protein adducts in the brain, two experiments were performed. In each experiment, neonatal rats were treated with either 60 mg/kg of APAP, 150 mg/kg of APAP, or saline control on postnatal (P) days 4 and 5. Two hours after treatment on P5, brain and liver were collected and analyzed using LC-MS/MS to quantify APAP-protein adducts. The second experiment used the same exposure paradigm for immunohistochemical analysis of cleaved caspase-3 expression and pyknotic body formation as indicators of cell death. Significant levels of APAP-protein adducts were detected in neonatal rat brains in both treatment groups. The APAP-protein adduct levels detected in the brains increased with dosage and in a manner proportional to APAP-protein adducts observed in the liver, suggesting that a toxicity reaction similar to APAP-induced liver toxicity may be occurring in the neonatal brains. Histological analysis also revealed a significant increase in cleaved caspase-3+ cells and pyknotic nuclei in the nucleus accumbens and prefrontal cortex. These results collectively indicate that the neonatal brain is a site of APAP metabolism that may be vulnerable to NAPQI-induced mediated injury during development. To further test the susceptibility of neonatal brain to APAP exposure, additional studies are underway to investigate APAP metabolism and oxidative stress markers in pregnant dams and their fetuses. These studies will determine whether the fully developed maternal liver can be protective against APAP metabolism in the fetal brain, separately from neonatal exposure.

Disclosures: A.C. Dungan: None. **J.W. VanRyzin:** None. **M. Devalapalli:** None. **J. Fagan:** None. **W. Parker:** None. **K.J. Reissner:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.08/D24

Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS Grant 5R01NS116054-05

Title: Neural stem cell cytokinesis remnants in vivo: trashcan or treasure?

Authors: *K. S. LETTIERI, N. D. DWYER;
Cell Biol., Univ. of Virginia, Charlottesville, VA

Abstract: Proper neural stem cell (NSC) division is essential for producing enough neurons to create a brain of appropriate size and function. Cortical NSCs form a polarized neuroepithelium with an apical membrane along the lateral ventricle. Early in development, NSCs divide symmetrically before switching to asymmetric neurogenic divisions. The balance of proliferation and neurogenesis determines the size and thickness of the cortex. Cortical NSCs undergo a polarized form of cell division which takes place at the apical membrane. The last step of cell

division, cytokinetic abscission, severs the intercellular midbody (MB) bridge connecting two daughter cells. After abscission, the center piece of the bridge, the midbody remnant (MBR), persists at the apical membrane. It is not known whether NSCs release MBRs into the ventricle, engulf them, or whether this changes in different modes of division. Defects in abscission have been linked to human brain malformations, and we have previously shown how loss of abscission protein Cep55 results in microcephaly, emphasizing the importance of abscission regulation during brain development. It is unknown how the MBR influences NSC divisions during brain development. Cell line studies suggest the MBR acts as a signaling organelle by promoting proliferation when engulfed. In embryonic cortex, we observed more MBRs at earlier ages where there are more symmetric NSC divisions. Others have suggested MBRs influence and promote primary ciliogenesis. Based on these data, we hypothesize that MBRs are released during symmetric divisions and engulfed by neighboring NSCs during asymmetric divisions. To visualize MBR formation, localization, and handling during brain development, we use a Kif23-EGFP BAC transgenic reporter mouse line. Kif23-EGFP localizes to the center of the MB and remains in the MBR after abscission. Using this line, we are able to visualize MBs and MBRs in embryonic cortices. We confirmed that the Kif23-EGFP transgene does not disrupt brain growth, and that Kif23-EGFP localizes properly to the center of the MB and MBRs. We also examined the number of MBRs en face on the apical membrane of brain cortices at different ages. To determine whether the MBRs play a role in the brain post-abscission, we will investigate whether the MBRs are engulfed by NSCs and how their post-abscission handling changes in the brain at early vs late ages. Additionally, we can examine how MBR handling changes when cytokinetic abscission is disrupted in the microcephaly mutant Cep55 since we observed increased MBRs at the apical membrane in these mutants. This will enable us to elucidate how MBRs affect brain development in vivo.

Disclosures: K.S. Lettieri: None. **N.D. Dwyer:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.09/D25

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Key Research and Development Program of China 2021YFA1101302
National Natural Science Foundation of China 32370852
National Natural Science Foundation of China U24A2014

Title: CHARM: A Morphomics Pipeline Decodes Radial Glia Morphogenesis and Scaffold Dynamics In Vitro

Authors: *X. CHEN[1], Y. LIU[1], L. MA[2];
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China; [2]Dept. of Anat. and Histology & Embryology, Sch. of Basic Med. Sci., Fudan Univ., Shanghai City, China

Abstract: Radial glial cell (RGC) morphology is integral to the spatiotemporal assembly and cytoarchitecture of the developing neocortex. However, modeling RGC morphogenesis in vitro remains constrained by the spatial limitations of conventional organoids and the reliance on low-dimensional, operator-dependent profiling methods.To address these limitations, we established a dual-scale in vitro platform, featuring extended human cortical organoids (ehCOs) that support macroscopic scaffold self-organization. By integrating this model with the computational pipeline CHARM (Clustering and High-dimensional Analysis of RGC Morphology), we assessed RGC morphological heterogeneity and investigated the role of Integrin αvβ8 (ITGB8) in cytoarchitectural scaffold assembly. Methodologically, CHARM utilizes a Random Forest classifier for RGC alignment to extract a 77-parameter morphological feature library. Subsequent UMAP and HDBSCAN clustering is constrained by a multi-metric scoring system to limit algorithmic overfitting. To evaluate underlying mechanisms, we applied lentivirus-mediated ITGB8 knockdown in the ehCO model, combined with bulk/snRNA-seq and spatial immunofluorescence. Baseline profiling of 1,180 RGCs described a morphological hierarchy characterized by cellular elongation and basal process arborization. Following ITGB8 knockdown, CHARM quantified a decrease in branching complexity and a restricted spatial distribution of basal processes. Transcriptomic and spatial analyses indicated that ITGB8 depletion altered cell-extracellular matrix (ECM) interactions. This reduction in matrix anchoring was associated with altered internal cytoskeletal tension, topological densification of the RGC scaffold, and decreased lateral spacing. These structural changes coincided with a reduction in the RGC proliferative pool and limited neuronal migration. In conclusion, application of the CHARM pipeline suggests that ITGB8 couples ECM anchoring with internal cytoskeletal tension, contributing to the maintenance of RGC scaffold topology during early corticogenesis.

Disclosures: X. Chen: None. **Y. Liu:** None. **L. Ma:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.10/D26

Topic: A.01. Neurogenesis and Gliogenesis

Support: KAKENHI JP26K09819
KAKENHI JP20K07237
KAKENHI JP18K14999

Title: Molecular machinery underlying Cyclin D2 mRNA transport in radial glial cells

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Abstract: Radial glial (RG) cells are highly polarized neural stem/progenitor cells (NSPCs) that generate cortical neurons and provide a scaffold for their radial migration during neocortical development. This polarity is accompanied by the asymmetric subcellular localization of specific molecules, including *Cyclin D2* mRNA, which encodes a key cell-cycle regulator and is enriched not only in the soma but also in the basal endfeet of RG cells. We previously showed that a cis-acting transport element within the 3′ untranslated region of Cyclin D2 mRNA is sufficient (Tsunekawa et al., EMBO J, 2012) and required (unpublished, but presented at SfN 2023) for its localization to RG basal endfeet. However, the trans-acting molecular machinery that mediates this transport remains largely unknown. Because kinesin motors drive microtubule-based cargo transport in polarized cells, we examined kinesin motor proteins enriched in the embryonic brain as candidate regulators of *Cyclin D2* mRNA localization in RG cells. Several kinesins were prominently expressed in NSPCs within the ventricular and subventricular zones and were also detected along RG fibers and in basal endfeet, suggesting their potential involvement in basal mRNA transport. To test their functional roles, we performed siRNA-mediated knockdown (KD) of selected kinesins by *in utero* electroporation in the embryonic mouse cortex, followed by fluorescence *in situ* hybridization to visualize *Cyclin D2* mRNA in GFP-labeled RG cells. KD of one candidate kinesin markedly reduced the accumulation of *Cyclin D2* mRNA in RG basal endfeet. These findings suggest that this kinesin contributes to the selective basal localization of *Cyclin D2* mRNA in RG cells. We are currently investigating RNA-binding proteins that may cooperate with this candidate motor protein to form a transport complex responsible for *Cyclin D2* mRNA delivery to basal endfeet. Together, this study provides new insight into the molecular mechanisms by which RG cells establish subcellular mRNA localization, a process that may contribute to spatially regulated cell-cycle control during cortical development.

Disclosures: T. Kikkawa: None. **S. Naher:** None. **N. Osumi:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.11/D27

Topic: A.01. Neurogenesis and Gliogenesis

Support: MH113257
MH129981
MH094589
NS089777
NS095654
MH106934
MH116488

MH110926
MH129981

Title: Development and evolution of the cortical sensorimotor-association axis

Authors: *J. TSYPORIN[1], M. ZHANG[1], C. QI[1], A. SEGAL[1], X. LI[2], I. PAVLOVIC[1], S. BANDIERA[1], T. FINN[4], S. KIM[1], A. SHIBATA[1], T. NAKAMURA[1], K. ONISHI[6], Z. ZHANG[7], N. SALLA[1], D. DOYLE[1], N. RUIZ-REIG[8], F. TISSIR[9], F. TISSIR[10], Y. NAKAGAWA[11], S. MA[12], K. T. GOBESKE[1], K. PATTABIRAMAN[3], T. SHIMOGORI[13], A. DUQUE[1], A. FORNITO[14], H. HUANG[7], B. CHEN[5], N. SESTAN[3];
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Abstract: The cerebral cortex is organized along a dominant sensorimotor-to-association (S-A) axis, anchored by modality-specific primary sensorimotor areas at one end and transmodal association areas forming distributed networks that support abstract cognition at the other. The developmental mechanisms shaping this axis remain elusive. Here, we present converging multispecies evidence supporting the Multinodal Induction-Exclusion in Network Development (MIND) model, in which S-A patterning is governed by competing processes of induction and exclusion driven by two opposing transcriptomically-defined programs. “Pericentral” programs are induced around fronto-temporal poles, progress inward toward central regions of the undifferentiated neocortex, and define higher-order association features. “Central” programs are induced centrally through first-order sensorimotor thalamocortical inputs, establish primary areas, and exclude pericentral programs. These conserved programs compete for space, resulting in compartmentalized expression of axon guidance, cell-cell adhesion, retinoic acid signaling, synaptogenesis, Wnt signaling, and autism risk genes. Notably, PLXNC1 and SEMA7A, a receptor-ligand pair representing pericentral and central programs, respectively, exhibit repulsive interactions between primary and higher-order association cortico-cortical axons. Induction and exclusion together establish an S-A organization in which primary areas emerge as focal islands within a broader ocean of distributed association networks. The MIND model provides a unifying framework for experimental, evolutionary, and clinical phenomena, revealing induction and exclusion as antagonistic yet complementary principles shaping the S-A axis and processing hierarchies.

Disclosures: J. Tsyporin: None. **M. Zhang:** None. **C. Qi:** None. **A. Segal:** None. **X. Li:** None. **I. Pavlovic:** None. **S. Bandiera:** None. **T. Finn:** None. **S. Kim:** None. **A. Shibata:** None. **T. Nakamura:** None. **K. Onishi:** None. **Z. Zhang:** None. **N. Salla:** None. **D. Doyle:** None. **N. Ruiz-Reig:** None. **F. Tissir:** None. **F. Tissir:** None. **Y. Nakagawa:** None. **S. Ma:** None. **K.T. Gobeske:** None. **K. Pattabiraman:** None. **T. Shimogori:** None. **A. Duque:** None. **A. Fornito:** None. **H. Huang:** None. **B. Chen:** None. **N. Sestan:** None.

Poster

PSTR210: Neuronal Differentiation and Circuit Maturation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR210.12/D28

Topic: A.01. Neurogenesis and Gliogenesis

Support: the National Natural Science Foundation of China (No.82501664)

Title: Embryonic microglia regulate Zfhx3$^+$ projection neuron differentiation during spinal cord development

Authors: *J. XU[1,2], Z. LI[3], S. YU[4], Y. LI[5];
[1]Xiangya Hospital, Central South Univ., Changsha, China; [2]Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China; [3]The Second Affiliated Hosp. of Anhui Med. Univ., Hefei, China; [4]Anhui Med. Univ., Hefei, China; [5]Neurol., Boston Children's Hosp., Shanghai, China

Abstract: Long-range projection neurons are essential for coordinating spinal motor circuits, but the non-neuronal niche signals that regulate their developmental specification remain incompletely understood. Zfhx3 marks a population of spinal long-range projection neurons that can support supraspinal-to-lumbar relay formation. We therefore asked whether developmental spinal cord microglia contribute to the generation of Zfhx3$^+$ projection neurons.During mouse spinal cord development, Iba1$^+$ microglia entered the embryonic spinal cord from E10.5-E14.5 when Zfhx3$^+$ neurons began to emerge. Single-cell transcriptomic profiling of embryonic spinal cord microglia revealed high expression of microglial identity and developmental-state features, including P2ry12, Tmsb4x and C1q, with limited expression of canonical adult injury-associated microglial genes such as Spp1, Lgals3 and Itgax. Immunostaining confirmed that embryonic spinal cord microglia expressed P2ry12, Tmsb4x, and C1q supporting their developmental microglial identity.
To test whether embryonic microglia are required for Zfhx3$^+$ neuronal differentiation, we analyzed microglia-deficient Csf1r^ΔFIRE/ΔFIRE mice and pharmacological microglial depletion models. Loss of microglia reduced the generation of Zfhx3$^+$ neurons in the developing spinal cord and altered neuronal differentiation programs revealed by single-nucleus RNA sequencing. In particular, microglial depletion reduced the proportion of long-range projection neuron-associated populations and decreased expression of Zfhx3-associated projection neuron genes, including Zfhx3, Zfhx4 and Foxp2. Moreover, we found that embryonic microglia co-culture promoted the Zfhx3$^+$ neuron differentiation of both mouse ESC and human iPSC-derives neural stem cells in vitro.
Together, these findings identify embryonic microglia as developmental regulators of Zfhx3$^+$ spinal projection neuron differentiation. More broadly, we suggest that developmental microglial provide a niche that can be redeployed to guide neural stem cell graft fate toward function-associated long-range projection neuron identities.

Disclosures: J. Xu: None. **Z. Li:** None. **S. Yu:** None. **Y. Li:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.02/D30

Topic: A.02. Stem Cells and Reprogramming

Title: Organoid Size Influences Electrical Activity of Surface Neurons on 2D Microelectrode Arrays

Authors: N. WILLIAMS[1], L. CHEW[1], S. A. LOUIS[1], A. EAVES[1,2], ***E. KNOCK**[1,3]; [1]STEMCELL Technologies Inc., Vancouver, BC, Canada; [2]Terry Fox Lab., BC Cancer, Vancouver, BC, Canada; [3]Biol., Simon Fraser Univ., Burnaby, BC, Canada

Abstract: Organoids derived from neural cells provide a human-relevant, physiological model for disease modeling and drug discovery. Multielectrode array (MEA) is being applied more frequently to investigate neural organoid activity. We sought to optimize a protocol for long-term culture and recording of organoids on MEA plates. We plated organoids on planar MEAs using the Axion Biosystems SpheroGuide MEA™ plates. We differentiated healthy control human induced pluripotent stem cells (hiPSCs) into guided organoids using STEMdiff™ Dorsal Forebrain differentiation Medium. Organoids were switched into complete BrainPhys™ hiPSC Neuron medium on day 43, then harvested and plated at one organoid per well on the MEA on day 77. Recordings were taken hourly for 24 hours after which the organoids were either collected and returned to suspension culture or maintained attached on the MEA plate until day 115. At day 115 the organoids in suspension were re-attached to the plate and the activity was recorded alongside the continuously attached organoids. In organoids that were continuously attached until day 115, we observed a decrease in average resistance and covered electrodes (32.18 ± 6.65 kOhms and 10.83 ± 1.83 electrodes at day 77 vs 24.83 ± 3.75 kOhms and 10.00 ± 3.16 electrodes at day 115; N = 6 organoids, 1 experiment). The mean firing rate and number of active electrodes in organoids after continuous attachment decreased notably compared to organoids that had been in suspension prior to being attached for recordings (0.08 ± 0.20 Hz and 1.67 ± 3.61 active electrodes in day-115 continuous attachment organoids, vs 0.81 ± 1.05 Hz and 4.17 ± 2.23 active electrodes in day-115 organoids which were in suspension prior to attachment, N = 6 organoids, mean ± STDEV, 1 experiment). Further analysis of day-77 recordings indicated that some electrode resistance values exceeded the threshold value (70 kOhms). We hypothesized that larger organoids were compressing the surface neurons and reducing activity. To test this, we plated organoids on top of electrically active neurons (> 1 Hz mean firing rate). We observed a trend towards decreasing mean firing rate with an organoid present (14.96 ± 3.65 Hz at baseline, falling to 4.42 ± 5.16 Hz 2 hours post-plating, N = 3 - 4 wells, 2 independent experiments). These results indicate that suspension-cultured organoids are more active than those organoids attached long-term on MEA plates. The reduced activity in the latter may be driven by compression-induced dampening of surface neuronal activity. Preliminary results demonstrate that

maintaining organoids in suspension between MEA recording sessions better maintains their neuronal activity levels.

Disclosures: N. Williams: A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **L. Chew:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **S.A. Louis:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **A. Eaves:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **E. Knock:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.03/D31

Topic: A.02. Stem Cells and Reprogramming

Title: Advancing Neurobiology Research with Complex Human iPSC-Derived CNS Co-Culture Models

Authors: G. S. SAHIN[1], R. L. ALLISON[1], C. FLIGOR[1], K. XU[1], ***S. SANKAR**[2], A. RAHMAN-ENYART[2], L. LIAN[3], D. SHANKAR[2], M. L. HENDRICKSON[1];
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Abstract: Human induced pluripotent stem cell (iPSC)-derived central nervous system (CNS) cell types are emerging as valuable tools designed to reduce reliance on animal models in biomedical research and drug discovery. However, due to the challenge of establishing mature co-cultures, many in vitro CNS models rely on individual cell types cultured in isolation, limiting the ability to capture the cellular complexities of the human brain. To address this limitation, we developed and validated complex iPSC-derived CNS co-culture models. Human iPSCs were differentiated into cortical glutamatergic neurons, astrocytes, oligodendrocyte progenitor cells (OPCs), and microglia and established in monoculture or in multiple co-culture configurations. Cellular identity, purity, and phenotypic consistency were confirmed using validated cell type-specific antibodies. Immunocytochemical analysis demonstrated robust expression of various markers in neurons, GFAP and Aquaporin4 in astrocytes, IBA1 in microglia, and MBP in oligodendrocytes in both monocultures and co-cultures, supporting the generation of physiologically relevant CNS cell populations. Compared with monoculture systems, complex co-culture models promoted extensive cell-cell communication and resulted in cellular morphologies that more closely resembled their in vivo counterparts. Neurons displayed enhanced neurite outgrowth and network complexity, astrocytes and oligodendrocytes adopted more mature stellate morphologies, and microglia exhibited highly ramified processes characteristic of surveillant states observed in vivo. Collectively, these findings demonstrate the utility of human iPSC-derived CNS co-culture systems as biologically relevant NAM platforms for studying neurobiology. The incorporation of multiple interacting human cell types provides

improved physiological relevance and supports their application in translational research and drug discovery workflows.

Disclosures: G.S. Sahin: A. Employment/Salary (full or part-time):; BrainXell. **R.L. Allison:** A. Employment/Salary (full or part-time):; BrainXell. **C. Fligor:** A. Employment/Salary (full or part-time):; BrainXell. **K. Xu:** A. Employment/Salary (full or part-time):; BrainXell. **S. Sankar:** A. Employment/Salary (full or part-time):; Proteintech. **A. Rahman-Enyart:** A. Employment/Salary (full or part-time):; Proteintech. **L. Lian:** A. Employment/Salary (full or part-time):; Proteintech. **D. Shankar:** A. Employment/Salary (full or part-time):; Proteintech. **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.04/D32

Topic: A.02. Stem Cells and Reprogramming

Support: NSF EFRI BEGIN OI

Title: Assembling 3D Functional Brain Tissue from Neural Spheroid Building Blocks in PCL Scaffolds

Authors: *L. DALIR[1], S. TATIC-LUCIC[2], Y. BERDICHEVSKY[2];
[1]Bioengineering, [2]Lehigh Univ., Bethlehem, PA

Abstract: Organoids are increasingly used to model the brain in vitro. Brain organoids have been applied to study the formation of connections between neurons, and the development of spontaneous activity patterns that are characteristic of healthy brain function. However, robust modeling of complex activity patterns such as oscillations and traveling waves has been challenging with existing organoid technologies. This is due to the random arrangement of neuron types within the organoid, leading to formation of highly variable circuits. In contrast, the brain is characterized by well-defined cytoarchitecture that consists of precise spatial arrangement of different neuron types. Here, we report a novel technology based on 3D printed scaffolds for creation of patterned brain organoids, and investigate how controlled excitatory/inhibitory cytoarchitecture shapes cortical wave dynamics.
Neural spheroids were formed from dissociated rat cortex or human iPSC-derived neurons co-cultured with rat astrocytes, and plated into the pores of 3D-printed polycaprolactone (PCL) scaffolds to form desired spatial patterns. To study how GABAergic neuron presence and spatial organization influence network dynamics, constructs were assembled from human iPSC-derived glutamatergic and GABAergic neurons as discrete building blocks, generating various distinct tissue configurations: uniform excitatory networks, uniform mixed excitatory/inhibitory networks, and constructs with spatially defined inhibitory-dense regions embedded within an excitatory population. Spontaneous and optogenetically evoked activity was recorded using

calcium imaging with jRGECO1a, with channelrhodopsin-2 (ChR2) used to evoke traveling waves in the constructs.
Scaffolded rat cortical constructs generated highly reproducible traveling waves of neural activity, including planar and complex wave patterns with propagation speeds comparable to those recorded in rat cortical slices. Building on this, we are extending the platform to human iPSC-derived neurons to examine how the presence of GABAergic neurons and their spatial arrangement within the construct, whether distributed uniformly or localized to defined regions, affects spontaneous network dynamics and wave propagation properties. This work underscores the potential of 3D-printed scaffold technologies to overcome the limitations of conventional organoid systems by enabling the design of cytoarchitecturally defined brain-like tissues, and provide a tractable model for examining how the presence and spatial distribution of inhibitory neurons shapes emergent cortical network dynamics.

Disclosures: L. Dalir: None. **S. Tatic-Lucic:** None. **Y. Berdichevsky:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.05/D33

Topic: A.07. Development of Neural Systems

Support: NIH Grant R01HD102534
NIH Grant T32NS096050

Title: The role of the ncBAF chromatin remodeler in the regulation of in vitro human neurodevelopment

Authors: *A. MUNIZ PEREZ, D. U. GORKIN;
Emory Univ., Atlanta, GA

Abstract: Mutations in genes that encode chromatin remodelers are among the most frequent monogenic causes of neurodevelopmental disorders (NDDs). Recently, several case reports and a genome-wide scan have identified *de novo*, putative loss-of-function mutations in *BICRA* in patients with idiopathic autism spectrum disorder, intellectual disability, and/or developmental delay. *BICRA* encodes an exclusive subunit of the newly-discovered non-canonical BRG1/BRM (ncBAF) chromatin remodeling complex, whose full assembly incorporates either BICRA or its paralog, BICRAL. Although genetic evidence indicates that ncBAF complex function is critical for human neurodevelopment, the cellular and molecular mechanisms regulated by ncBAF are not well understood. Here, we investigate the role of ncBAF in regulating hiPSC pluripotency using isogenic human induced pluripotent stem cell (hiPSCs) that were gene edited to express heterozygous or homozygous null alleles in *BICRA* or *BICRAL.* We find that *BICRA* null, but not *BICRAL* null, hiPSCs are prone to spontaneous differentiation around colony borders. Bulk ATAC- and RNA-seq analyses indicate that *BICRA* null hiPSCs exhibit reduced chromatin

accessibility at pluripotency-related transcription factor binding motifs, along with elevated expression of genes related to neuronal differentiation and forebrain development. Current work is focused on performing transcriptomic and epigenomic phenotyping of our *BICRAL* null hiPSCs, as well as differentiating our *BICRA* and *BICRAL* null hiPSCs into three-dimensional neural organoids. Together, our data suggests that BICRA- and BICRAL- containing ncBAF complexes have distinct, non-redundant roles in regulating hiPSC pluripotency, underscoring the need to define how changes in protein complex stoichiometry affects genomic targeting and chromatin remodeler function.

Disclosures: A. Muniz Perez: None. **D.U. Gorkin:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.06/D34

Topic: A.02. Stem Cells and Reprogramming

Title: Enabling clinical translation of iPSC-derived midbrain dopaminergic neuron progenitors using GMP-grade reagents

Authors: *B. ETTESTAD, C. SAGARSKY, X. LU, H. HINTZ, J. HAGEN, D. BHUIYAN, C. HEGER;
R&D Systems, Minneapolis, MN

Abstract: Neurodegenerative diseases such as Parkinson's disease (PD) remain difficult to treat due to the limited regenerative capacity of the central nervous system. Recent advances in stem cell-based therapies have enabled the development of restorative approaches aimed at replacing lost neuronal populations. However, the clinical translation of these therapies requires robust and reproducible workflows using GMP-compatible materials. We implemented an established dual-SMAD inhibition protocol, employing a comprehensive range of GMP-grade reagents to differentiate human induced pluripotent stem cells (iPSCs) into midbrain dopaminergic neuron (mDA) progenitors. Cells were characterized at key stages using flow cytometry, immunocytochemistry (ICC), and automated capillary Western blotting. By Day 16, flow cytometry analysis showed the differentiated cells highly expressed markers consistent with the mDA progenitor phenotype, including FOXA2 (mean = 90.5%) and the neuron-specific cytoskeletal protein TUBB3 (mean = 66.6%) with no expression of the neural stem cell marker, PAX6 (mean = 0.55%) or the pluripotency marker, Nanog (mean = 0.63%). Cells matured for an additional 5 days prior to fixation and ICC analysis. On Day 21, cultures displayed consistent neuronal morphology and expression of the dopaminergic marker tyrosine hydroxylase (TH) (**Figure 1**). Automated Western blot analysis further confirmed robust TUBB3 and TH expression, with marked increases observed between Days 16 and 21. Together, these findings demonstrate a reproducible and translational workflow for the generation of mDA progenitors from human iPSCs using GMP-grade reagents supported by automated analytical platforms.

These methods enable the continued development of stem cell-based therapies for neurodegenerative diseases in both research and clinical settings.

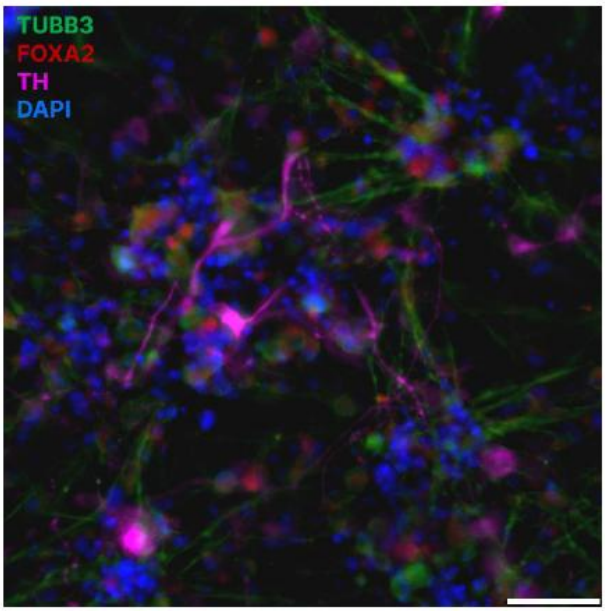


Figure 1. Representative image of cells stained for characteristic markers of mDA progenitors, TUBB3 (green) and FOXA2 (red), and the dopaminergic neuron marker tyrosine hydroxylase (TH, magenta). Scale bar = 50 µm.

Disclosures: B. Ettestad: A. Employment/Salary (full or part-time):; R&D Systems. **C. Sagarsky:** A. Employment/Salary (full or part-time):; R&D Systems. **X. Lu:** A. Employment/Salary (full or part-time):; R&D Systems. **H. Hintz:** A. Employment/Salary (full or part-time):; R&D Systems. **J. Hagen:** A. Employment/Salary (full or part-time):; R&D Systems. **D. Bhuiyan:** A. Employment/Salary (full or part-time):; R&D Systems. **C. Heger:** A. Employment/Salary (full or part-time):; R&D Systems.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.07/D35

Topic: A.02. Stem Cells and Reprogramming

Title: Functional Characterization of L-DOPA Responses in Midbrain Organoids Using 3D HD-MEA Technology

Authors: *B. L. W. SWEETEN[1], X. HAN[2,3], R. YOKOI[2,3], B. NODA[2,3], I. SUZUKI[2,3]; [1]3Brain US LLC, Franktown, CO; [2]Tohoku Inst. of Technol., Sendai, Miyagi, Japan; [3]VitroVo Inc., Sendai, Miyagi, Japan

Abstract: The development of brain organoids has opened a powerful avenue for modelling the richness and complexity of human neural circuitry *in vitro*. Neural network dysfunction can be a hallmark of many prevalent neurological disorders, therefore, the ability to investigate the

functional network activity of brain organoids is becoming essential for therapeutic development. Yet, dissecting the functional organization of these complex 3D structures remains technically challenging. Here, we present an approach built on 3Brain's CorePlate™ 3D, a next-generation high-density multielectrode array (HD-MEA) platform engineered to capture and analyse the electrical dynamics of three dimensional neural tissues such as brain organoids. CorePlate™ 3D enables the simultaneous acquisition of signals from thousands of electrodes with a high signal-to-noise ratio, offering unprecedented access to the spatial and temporal features of 3D neuronal networks. Using this platform, we functionally characterized a four month old midbrain organoid and investigated its response to varying concentrations of L-3,4dihydroxyphenylalanine (L-Dopa). From these recordings, we extracted single unit spikes and isolated the activity of individual putative neurons embedded within the organoid's architecture. L-Dopa application induced pronounced changes across multiple functional metrics, including firing rate, burst structure and network connectivity, clearly demonstrating the sensitivity of CorePlate™ 3D to modulatory effects ranging from single cell physiology to large scale network dynamics. Overall, our findings establish 3Brain's CorePlate™ 3D as a robust and versatile technology for unlocking the full functional potential of midbrain organoids, positioning it as a powerful tool for mechanistic research, disease modelling, and drug development.

Disclosures: B.L.W. Sweeten: None. **X. Han:** None. **R. Yokoi:** None. **B. Noda:** None. **I. Suzuki:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.08/D36

Topic: A.02. Stem Cells and Reprogramming

Support: Foundation for Prayer Willis Research, Research Award

Title: Fine-Tuning SHH Signaling Generates Hypothalamic Nucleus-Enriched Organoids for Modeling the Developmental Assembly of Hypothalamic Feeding Circuitry

Authors: *J. NAM, F. BIREY;
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Abstract: The hypothalamus is a critical brain region that regulates the autonomic nervous system and energy homeostasis. Distinct hypothalamic nuclei, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), and ventromedial hypothalamus (VMH), form interconnected circuits that coordinate physiological and behavioral responses to nutritional status. Despite their central role in metabolic regulation, the developmental mechanisms underlying the specification of distinct hypothalamic nuclei remain poorly understood. To investigate human hypothalamic development and establish an in vitro model of hypothalamic nuclei, human hypothalamic organoids were exposed to varying concentrations of Smoothened

Agonist (SAG) and Purmorphamine (PM), two agonists of the Sonic Hedgehog (SHH) signaling pathway. Quantitative PCR analysis revealed that modulation of SHH signaling generated distinct transcriptional profiles corresponding to dorsal and ventral hypothalamic identities. Bulk RNA sequencing further demonstrated that increased SHH signaling promoted the expression of ventral hypothalamic markers, including TBX2, POMC, SOX14, and GABRA5, which are associated with ARC- and VMH-like identities. In contrast, reduced SHH signaling enriched the expression of dorsal hypothalamic markers, including NHLH2, XBP1, and UNCX, consistent with PVN-like specification. Transcriptomic profiling and principal component analysis further identified optimal SHH signaling conditions that preferentially generate ARC-, VMH-, and PVN-like hypothalamic organoids. To investigate circuit formation between distinct hypothalamic regions, assembloids were generated by fusing hypothalamic organoids patterned under different SHH signaling conditions. The resulting assembloids maintained clear spatial boundaries while remaining structurally integrated, and axonal projections were observed extending between neighboring organoid domains. These assembloids recapitulated key features of spatial organization and directional neuronal connectivity between distinct hypothalamic regions. Together, these findings demonstrate that graded SHH signaling directs the specification of ARC-, VMH-, and PVN-like hypothalamic identities in human organoids and enables the assembly of region-specific hypothalamic circuits in vitro. This platform provides a scalable human model for studying hypothalamic development, feeding-circuit formation, and the pathogenesis of metabolic disorders associated with hypothalamic dysfunction.

Disclosures: J. Nam: None. **F. Birey:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.09/D37

Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant R01DA052284 to IKS and SLC
NIH Grant R03 AA031535-01 to SLC

Title: A Stage-Resolved Transcriptomic and Cellular Atlas of Human Cerebral Organoid Development Reveals Developmental Windows of Ethanol Vulnerability

Authors: *M. BISHIR[1], W. HUANG[1], I. K. SARIYER[2], S. L. CHANG[1];
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Abstract: Prenatal alcohol exposure disrupts fetal brain development; however developmental stage-specific vulnerability of the human brain remains poorly characterized. Human cerebral organoids (hCOs) provide a human-relevant model that recapitulates key stages of development

and enables investigation of ethanol (EtOH)-induced neurodevelopmental perturbations.To define the molecular and cellular trajectory of hCO development, we generated a stage resolved transcriptomic and cell-type atlas spanning Days 10, 20, 30, 40, 60, and 80 of hCO growth with and without EtOH exposure (0/50 mM, 24h). Integration of mRNA/lncRNA sequencing, flow cytometry, Allen Human Fetal Brain Atlas alignment, and machine-learning-based developmental prediction identified stage specific transitions from neuroepithelial expansion through neurogenesis, gliogenesis, and myelination, accompanied by stage-specific shifts in progenitor, neuronal, glial, and oligodendrocyte populations. Developmental age was accurately predicted across stages using a Random Forest regression model (R^2=0.908, RMSE=7.29 days), supporting the biological fidelity of the atlas.EtOH elicited distinct stage-dependent molecular and cellular vulnerability signatures across all developmental stages examined, with maximal susceptibility at Day 40 (2,115 DEGs). During intermediate stages, hCO maturation (days 20-30) and gliogenesis (day 60), EtOH induced depletion of PAX6+ radial glial progenitors, inhibition of LXR/RXR and cholesterol-IGF signaling, and activation of neuroinflammatory pathways marked by increased CD11B+ microglial and CD184+ astrocytic populations, highlighting dynamically evolving vulnerability throughout development. During neuroepithelial expansion (Day 10), EtOH activated HOTAIR-mediated Wnt/β-catenin signaling, driving premature progenitor differentiation and reducing SOX2+, Ki67+, CD71+, and CD29+ populations. During peak neurogenesis (Day 40), EtOH suppressed synaptogenesis, GABAergic, and axonal guidance pathways, accompanied by reduced proliferative cell populations and compensatory upregulation of adhesion-related markers. During early myelination (Day 80), EtOH inhibited cholesterol biosynthesis and myelination associated pathways, indicating persistent disruption of oligodendrocyte maturation.Together, these findings establish a stage-resolved transcriptomic and cellular atlas of hCO development that delinates temporally distinct windows of EtOH-induced vulnerability during human fetal brain development, from neuroepithelial progenitor maintenance and neurogenesis to impairment of myelination programs.

Disclosures: M. Bishir: None. **W. Huang:** None. **I.K. Sariyer:** None. **S.L. Chang:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.10/D38

Topic: A.07. Development of Neural Systems

Title: A Defined 3D Platform for Floor Plate Neuroepithelium Induction from Human iPSCs Using VitroGel® Hydrogels and RocketCell™ Media, with Cryopreservable Neural Spheroids

Authors: *J. HUANG[1], R. I COHEN[2];
[1]TheWell Biosci. Inc, Monmouth Junction, NJ; [2]TheWell Bioscience, Inc., Monmouth Junction, NJ

Abstract: The directed differentiation of iPSCs into relevant neural subtypes requires precise temporal control of morphogenetic signaling within an environment that recapitulates the 3D architecture of the developing neural tube. Floor Plate Neuroepithelium (FPNE), the ventral midline organizer of the neural tube, is an essential intermediate for generating numerous neuronal cell types, including dopaminergic neurons, serotonergic neurons, motor neurons, and interneurons. Standard 2D protocols for FPNE induction are limited by cellular heterogeneity, poor spatial organization, and inconsistent morphogen exposure inherent to 2D culture. Here we present an optimized 3D induction system employing **VitroGel® STEM** and **NEURON** hydrogels together with **RocketCell™** NSC media to stepwise progress iPSC spheroids to FPNE. IPSCs established in **VitroGel® STEM** were patterned through 3 defined stages using RocketCell™ NSC Xeno-Free Medium and Supplement together with 3 sequentially used small molecule cocktails: RocketCell™ FPNE1 (establishing); FPNE2 (propagating), and FPNE3 (patterning). The 3D microenvironment provided by **VitroGel® STEM** maintained compact, uniform colonies across all FPNE stages, enabling coherent collective responses to morphogen gradients that are less reproducibly achieved in dissociated 2D monolayers. Following FPNE3 patterning, spheroids were transferred to **VitroGel® NEURON** for precursor and terminal differentiation, yielding cells positive for β-III-tubulin and markers of dopaminergic (TH^+) and cholinergic ($ChAT^+$) lineages, reflecting the broad multipotency of ventral FPNE-derived progenitors. Other neuronal subtypes accessible from FPNE patterning include serotonergic, GABAergic, and spinal motor neurons. The **VitroPrime™ 3D Culture and Imaging Plate** facilitated high-resolution imaging through each differentiation stage without sample transfer or gel disruption. Critically, FPNE spheroids at any stage were cryopreserved using DMSO-based freeze media supplemented with **RocketCell™ Cell Viability Enhancer**, a proprietary 1000× small molecule cocktail that significantly outperformed ROCK inhibitor alone in post-thaw metabolic recovery and colony-forming efficiency. Frozen FPNE spheroids were thawed and successfully re-entered downstream differentiation protocols without loss of patterning identity, establishing a bankable and reproducible neural progenitor intermediate for scaled production. This platform provides a scalable, xeno-free route from iPSC to regionally specified neural progenitors with broad applicability in disease modeling, drug discovery, and regenerative medicine.

Disclosures: J. Huang: None. **R. I Cohen:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.12/D40

Topic: A.02. Stem Cells and Reprogramming

Support: NIH 1R21NS138850-01A1

Title: Rapid and Efficient Lower Motor Neuron Differentiation from hiPSCs Using a Hybrid Protocol

Authors: *E. S. LAWTON[1], N. TEANEY[2], N. IYER[3];
[1]Tufts Grad. Sch. of Biomed. Sci., Medford, MA; [2]Neurobio., Tufts Univ. Sch. of Medicine, Dept. of Neurosci., Medford, MA; [3]Biomed. Engin., Tufts Univ., Medford, MA

Abstract: Generating spinal motor neurons (MNs) from human induced pluripotent stem cells (hiPSCs) is of particular interest for disease modeling and therapeutic discovery as these cell populations are inaccessible from living donors. Transcription factor (TF) induction offers a fast and efficient approach to MN differentiation; notably, the NIL combination (NGN2, ISL1, LHX3) is a promising strategy to generate putative lower MNs. However, these TF-induced MNs do not express key markers for spinal MN identity and function, including HOX genes that specify rostrocaudal positional identity. Direct differentiation using small molecules can more faithfully impose spinal identity, but methods remain lengthy, complex, and costly. Here we describe a "hybrid" differentiation protocol that combines the speed and efficiency of TF-based induction with targeted small molecule patterning to confer caudal spinal neuron identity. Using the PiggyBac transposon system, a human NIL cassette (hNIL) was inserted under a doxycycline promoter into Kolf 2.1J hiPSCs. We verified that polyclonal pools that successfully integrated hNIL expressed pluripotency markers Oct3/4 and Ki-67 by immunocytochemistry (ICC). After a baseline protocol of 9 days of treatment with doxycycline and the Notch signaling inhibitor DAPT, cultures demonstrated distinct MN morphology and expressed pan-neuronal marker β-tubulin III (100%+ cells, n=2 technical replicates) and MN-specific transcription factors ISL1 and MNX1 (41% ISL1+, 12% MNX1+, 12% both). 14 days after induction, neurons exhibited spontaneous activity detected by Microelectrode Array (14.3 spikes/min, n=1). To promote caudalization, the protocol was modified with the addition of Retinoic Acid, as well as dual SMAD inhibition by SB-435142 and LDN-193189, and Wnt signaling inhibition with CHIR99021. These cultures expressed pan-neuronal markers β-tubulin III (100% + cells, n=2 technical replicates) and MN-specific transcription factors ISL1 and MNX1 (42% ISL1+, 24% MNX1+, 17% both) after 6 days. These cells will be assessed via qRT-PCR for HOXA1, HOXB4, HOXC6, and HOXC9 to confirm rostrocaudal identity. This approach will also enable characterization of caudal MN diversity, including PHOX2B-expressing visceral MNs. Further applications include using this protocol in diseased cell lines and patient-derived stem cells, or for generating spinal MNs in cocultures and organoids. These functional and transcriptionally active lower MNs provide a scalable platform to quickly and efficiently study motor neurons in the brainstem and spinal cord.

Disclosures: E.S. Lawton: None. **N. Teaney:** None. **N. Iyer:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.13/D41

Topic: A.02. Stem Cells and Reprogramming

Title: Scalable Directed Differentiation of Human iPSC-Derived Oligodendrocyte Progenitor Cells for Functional Myelination and Drug Screening

Authors: ***J. MA**[1], M. GEORGE[2], C. W. MCMAHON[2], S. SCHACHTELE[2], J. LIU[2];
[1]Fujifilm Cell. Dynamics, madison, WI; [2]FUJIFILM Cell. Dynamics, Madison, WI

Abstract: Oligodendrocytes, the myelinating cells of the central nervous system (CNS), ensheathe neuronal axons to improve action potential conduction, velocity, and network communication. Human induced pluripotent stem cell (iPSC)-derived oligodendrocytes are a promising tool for improving drug screening for demyelinating disorders, including multiple sclerosis (MS) and stroke-related brain injury. While transcription factor-based protocols have accelerated the workflow and efficiency of oligodendrocyte differentiation, genetic manipulation circumvents normal developmental cues which may impact cell function as well as draw added scrutiny during regulatory review for therapeutic uses. In this study, we characterize and functionally evaluate human iPSC-derived oligodendrocyte progenitors (OPCs) differentiated using a rapid, serum-free, and scalable protocol directed with growth factors and small molecule inhibitors. Directed differentiation of OPCs resulted in cells that are highly pure and exhibit lineage maturity (>80% O4+, Olig2+, and Sox10+) immediately post-thaw. Evidence of functional maturity at thaw is presented, showing approximately 30-50% of cells expressing myelin basic protein (MBP) which remained stable for at least two weeks in monoculture, providing an extended myelination assay window without additional post-thaw maturation steps. In response to inflammatory stimulation (LPS, TNF α, and IFN γ), OPCs in monoculture show a 20% decrease in the percentage of MBP-positive cells and a 40% reduction in MBP expression area. This response is initiated as early as 24 post-thaw, demonstrating OPCs have a rapid neuroinflammatory response that can be utilized in demyelination drug-screening assays. Furthermore, known pro-myelinating compounds (Tasin-1, and ketoconazole) partially recover MBP expression following inflammatory stimulation, again demonstrating their relevance for promyelinating compound drug discovery. In co culture with iPSC-derived excitatory neurons or iPSC-derived motor neurons, significant colocalization of MBP with neuronal axons (Neurofilament-H) occurs within three weeks, indicative of myelination capability. These data demonstrate that human iPSC-derived OPCs manufactured at scale are highly pure and recapitulate human oligodendrocyte function. These cells provide an assay ready platform for remyelination drug discovery, neuroinflammation studies, and human relevant modeling of myelin biology.

Disclosures: J. Ma: None. **M. George:** None. **C.W. McMahon:** None. **S. Schachtele:** None. **J. liu:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.14/D42

Topic: A.02. Stem Cells and Reprogramming

Title: Frozen Microglia Derived from the Control SCTi003-A Induced Pluripotent Stem Cell Line Are Functional and in a Non-Activated State Post-Thaw.

Authors: J. CHAN[1], A. MOOSA[1], K. WRIGHTSON[1], D. OWANGO[2], A. GAFFNEY[1], ***J. OKUBO**[1], S. A. LOUIS[1], A. EAVES[1,3], E. KNOCK[1];
[1]STEMCELL Technologies Inc., Vancouver, BC, Canada; [2]Canventa Life Sci., Emeryville, CA; [3]Terry Fox Lab., Vancouver, BC, Canada

Abstract: Neuroinflammation is a hallmark of neurodegenerative disease and can increasesusceptibility to disease. To create human-relevant neuroinflammation models, wegenerated assay-ready human pluripotent stem cell (PSC)-derived microglia. Wedifferentiated the healthy control SCTi003-A PSC line into microglia using a serum-free,in-house protocol optimized for large-scale manufacturing and cryopreservation.Cryopreserved microglia were thawed into STEMdiff™ Microglia Maturation Medium,alongside unfrozen iPSC-derived microglia, for characterization. Microglia identity wasassessed by flow cytometry at days 0 and 10 post-thaw for CD45, CD11b, P2RY12, andTREM2 expression. To assess the activation state, spent media were collected at days2, 10, and 20 from both thawed and fresh cells. The reactive response was assessed byexposing microglia to 100 ng/mL lipopolysaccharide (LPS) or water (control) for 24hours and analyzing TNF-α and IL-6 in the spent media using a DuoSet™ ELISA.Phagocytic function was assessed with microscopy by examining uptake of pH-sensitivebioindicator particles at 1 and 24 hours. Microglia were also co-cultured with PSC-derived neurons and astrocytes for 7 or 20 days, and assessed by immunochemistry forexpression of MAP2 (neurons), IBA1 (microglia), and GFAP (astrocytes). We observed> 70% CD45+CD11b+, > 95% P2RY12+ and > 90% TREM2+ expression in microgliapost-thaw (N = 5). The spent media at 2, 10, and 20 days post-thaw fell below thedetection limit for TNF-α (15 pg/ml) and IL-6 (10 pg/ml) ELISAs (N = 2 - 5) indicatingthese microglia are non-reactive. The cells responded to 24-hour LPS treatment with asignificant increase in TNF-α and IL-6 secretion compared to control ($p < 0.001$ and $p < 0.0001$, respectively, N = 5). We observed uptake of the pH-sensitive bioparticles atboth 1 and 24 hours post-treatment (N = 3), indicating active phagocytosis. Lastly,IBA1+ microglia displayed a ramified morphology and close interaction with the GFAP+astrocytes after 7 and 20 days of co-culture (N = 2). Collectively, our data show that thehealthy, control SCTi003-A- iPSC line derived cryopreserved microglia are functional,and are in a non-activated state post-thaw, making them suitable for neuroinflammationmodeling in vitro.

Disclosures: J. Chan: A. Employment/Salary (full or part-time):; STEMCELL. **A. Moosa:** A. Employment/Salary (full or part-time):; STEMCELL. **K. Wrightson:** A. Employment/Salary (full or part-time):; STEMCELL. **D. Owango:** None. **A. Gaffney:** A. Employment/Salary (full or part-time):; STEMCELL. **J. Okubo:** A. Employment/Salary (full or part-time):; STEMCELL. **S.A. Louis:** A. Employment/Salary (full or part-time):; STEMCELL. **A. Eaves:** A. Employment/Salary (full or part-time):; STEMCELL, Terry Fox Laboratory. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); STEMCELL. **E. Knock:** A. Employment/Salary (full or part-time):; STEMCELL.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.15/D43

Topic: A.02. Stem Cells and Reprogramming

Support: Tufts Department of Biomedical Engineering Start-up
NIH DP2NS140734-01

Title: HIGH-EFFICIENCY GENERATION OF TRUNK NEURAL CREST CELLS FROM HUMAN PLURIPOTENT STEM CELLS AS A PLATFORM FOR PERIPHERAL NERVOUS SYSTEM MODELING

Authors: *Z. LIAO[1,2], I. CABOT[3,2], J. CHOW[2], L. MOSS[2], N. IYER[2];
[2]Biomed. Engin., [1]Tufts Univ., Medford, MA; [3]Amgen, Cambridge, MA

Abstract: Cell types in the peripheral nervous system (PNS) come from neural crest cells across multiple rostrocaudal axial regions, including the cranial, vagal, trunk, and sacral regions. However, trunk neural crest (TNC)-derived populations, including dorsal root ganglia sensory neurons, sympathetic neurons, and Schwann cells, remain inaccessible to current human pluripotent stem cell (hPSC) differentiation methods. Most existing neural crest protocols default to cranial identity, while protocols that target caudal regions have modest differentiation efficiencies (60-75%) or require labor-intensive cell-sorting. Addressing these gaps, we developed a low-labor method for differentiating high-purity TNCs, then demonstrated that they could be directed into trunk PNS cell types. To differentiate the TNCs, we first used our previously established method to pattern SOX2+/BRACHYURY+ neuromesodermal progenitors that express cervicothoracic HOX genes (HOXC6 and HOXC9), then optimized BMP, Wnt, and TGFβ signaling factors for neural crest induction. By DIV15, cultures yielded >96% SOX10+ (SRY-box transcription factor 10, a neural crest marker) cells, remained negative for spinal marker PAX6, and maintained HOXC6 and HOXC9 expression. To confirm PNS potential of the TNCs, we differentiated TNCs into neuronal and glial lineages. After sensory differentiation (DIV22), 100% of PRPH+ neurons expressed ISL1 and BRN3A. AraC treatment enriches the neuronal population to 95%, comparable to existing methods. By DIV29, these sensory neurons matured into TRPV1+/NaV1.7+/CGRP+ nociceptors. On microelectrode arrays (MEA), the nociceptors displayed sporadic baseline firing and a 1.5-fold firing rate upon capsaicin treatment. Calcium imaging also confirmed this stimulus-evoked response at the single-cell level. By DIV22 under sympathetic differentiation, 73.3% of cells were PHOX2B+ and subsequently expressed other sympathetic markers such as TH and ChAT. The sympathetic neurons showed rhythmic synchronized bursts on the MEA and had tripled firing rate in response to nicotine. Schwann cells (SCs) matured by DIV63, at which point 100% of the cells expressed MBP. Co-culturing SCs with nociceptors restored growth factor-depleted cultures back to baseline activity levels. This robust, high-efficiency platform substantially advances current protocols by generating regionally specified TNCs without manual picking, transgene expression, or cell-sorting. It provides a foundation for developing physiologically relevant and functional tissue-engineered models of the trunk PNS and its associated diseases, such as peripheral neuropathy and neuroblastoma.

Disclosures: Z. Liao: None. **I. Cabot:** None. **J. Chow:** None. **L. Moss:** None. **N. Iyer:** None.

Poster

PSTR211: Modeling Development *In Vitro*

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR211.16/D44

Topic: A.02. Stem Cells and Reprogramming

Title: Advancements in Modeling a Tri-Partite Neuromuscular Junction Using Human-Induced Pluripotent Stem Cell Derived Skeletal Myoblasts, Motor Neurons, and Schwann Cell Precursors

Authors: *T. KNOX, V. TRUONG, P. WALSH;
Anatomic Inc., Minneapolis, MN

Abstract: Skeletal muscle comprises approximately 40% of the human body and plays an essential role in a wide range of bodily systems, including metabolic, musculoskeletal, and neuromuscular. The neuromuscular junction (NMJ), which connects motor neurons to skeletal muscle fibers, is of particular interest for studying neurotoxins such as botulinum toxin, and neuromuscular diseases such as amyotrophic lateral sclerosis (ALS). Here, we introduce a novel method of producing human-induced pluripotent stem cell (hiPSC)-derived skeletal myoblasts, which can be used in combination with hiPSC-derived motor neurons (MNs) and Schwann cell precursors (SCPs) to model the NMJ and relevant diseases. This fully hiPSC-derived, single donor model provides a versatile system for testing pharmaceutical agents and developing therapeutics. Using a novel, 7-day directed differentiation protocol, we generated MYOD1 skeletal myoblasts through the exclusive use of growth factors and small molecules to direct cell fate. These myoblasts successfully underwent myogenesis, further differentiating into multinucleated myotubes, and then maturing into striated myofibers exhibiting spontaneous contractions. Throughout maturation, the cells expressed expected ICC markers including MyoD, Desmin, MyoG, and sarcomeric Titin. qPCR and bulk RNA sequencing further confirmed skeletal muscle identity and progressive maturation. To demonstrate broad applicability, we evaluated myoblast myogenesis and NMJ formation in both 2D and 3D conditions. In 2D, skeletal muscle cells were seeded in microfluidic compartmentalized chips across from MNs and SCPs. MNs extended axons through the microchannels onto the muscle while the SCPs exhibited a terminal Schwann cell-like morphology around the synapse. In 3D aggregates containing skeletal muscle, MNs, and SCPs, the co-cultures exhibited areas of spontaneous contractions for more than 2 months in culture, demonstrating the potential for long-term studies. We present a fast, scalable, and genetically unmodified approach for generating skeletal myoblasts. When combined with hiPSC-derived MNs and SCPs, these cells enable the construction of fully human neuromuscular systems that can be used to study NMJ biology, model neuromuscular diseases, and accelerate therapeutic discovery.

Disclosures: T. Knox: A. Employment/Salary (full or part-time):; Anatomic Incorporated. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership

Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.01/E1

Topic: A.08. Adolescent Development

Support: CONACYT grant CF-2019-6390
DGAPA-PAPIIT-UNAM IN208622
DGAPA-PAPIIT-UNAM IN212624

Title: Parental bonding is associate with childhood trauma and internalizing symptoms in a mexican twin sample

Authors: *E. ZALDÍVAR MORALES[1], D. RAMÍREZ GONZÁLEZ[3], M. FLORES-RAMOS[4], I. ESPINOSA MÉNDEZ[5], T. V. ROMAN-LOPEZ[6], M. E. RENTERÍA[7], A. MEDINA-RIVERA[8], A. E. RUIZ-CONTRERAS[2], S. ALCAUTER[9];
[1]Univ. Nacional Autonoma de Mexico, Mexico, Mexico; [2]Lab. Neurogenomica Cognitiva, Fac. Psicologia, Univ. Nacional Autonoma de Mexico, D.F., Mexico; [3]UNAM, Juriquilla, ; [4]Inst. Nacional de Psiquiatría Ramón de la Fuente, Ciudad de México, Mexico; [5]Inst. de Neurobiología, UNAM, Querétaro, Mexico; [6]Inst. de Neurobiologia, UNAM, Ciudad de Mexico, Mexico; [7]Brain & Mental Hlth. Program, QIMR Berghofer Med. Res. Inst., Herston, Australia; [8]Lab. Internacional de Investigación sobre el Genoma Humano, Univ. Nacional Autónoma de México, Queretaro, Mexico; [9]Neurobiología Conductual y Cognitiva, Inst. De Neurobiologia. Univ. Nacional A, Queretaro, Mexico

Abstract: Childhood trauma is a major risk factor for psychopathology and is strongly shaped by the early environment. Although lacking parenting styles are linked to internalizing symptoms, mapping the genetic vulnerabilities interacting within Latin American populations remains limited. Twin designs provide a unique opportunity to disentangle environmental and genetic influences on these associations. Data from 1,580 Mexican adults (29.92 ± 12.06 years old), 75% women, was obtained from the Mexican Twin Registry, TwinsMX. Participants completed the short form of the Childhood Trauma Questionnaire (CTQ), Parental Bonding Instrument (PBI), and self-reports of anxiety and depression. The PBI assessed maternal and paternal dimensions of care and overprotection. Associations of CTQ, PBI, and psychiatric symptoms were examined using mixed models analyses. Parenting style quadrants derived from PBI scores (optimal parenting, affectionate constraint, affectionless control, and neglectful parenting) were additionally compared according to childhood trauma exposure and severity. Higher childhood

trauma scores were significantly associated with increased anxiety and depressive symptoms. Lower parental care and higher parental overprotection were associated with higher CTQ scores. Maternal care showed the strongest inverse association with childhood trauma severity (Fig 1A), followed by paternal care (Fig 1C). Maternal overprotection was positively associated with CTQ severity (Fig 1B), whereas paternal overprotection showed no significant association (Fig 1D). Across both maternal and paternal models, participants classified within the low care/high overprotection reported the highest CTQ scores compared with other quadrants. These findings suggest that childhood trauma is associated with parental bonding patterns marked by emotional warmth and overprotection and is also linked to internalizing symptoms.

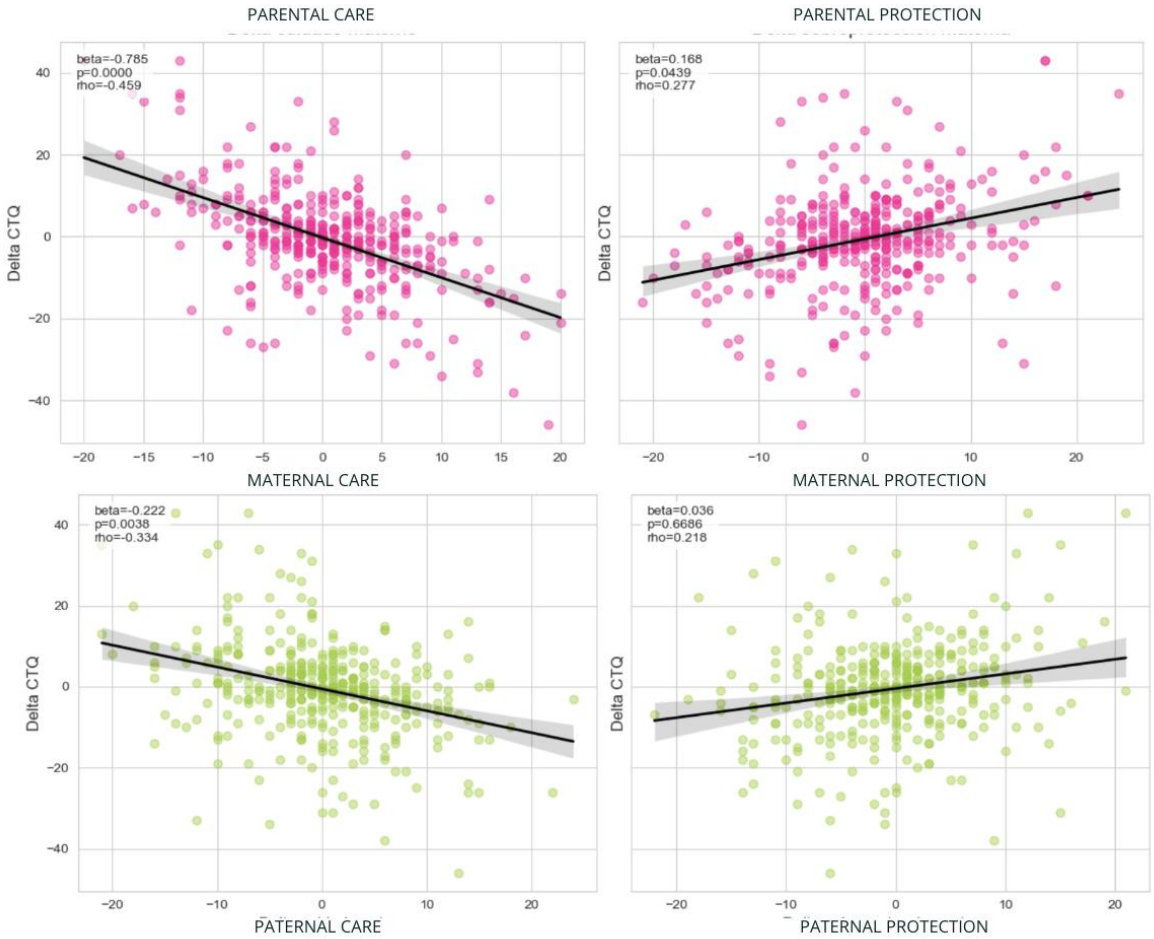


Figure 1. Association between parenting style and childhood trauma severity across paternal and maternal dimensions. Mixed effects models adjusting for zygocity. (A, C) Inverse relationship showing that lower levels of perceived are strongly correlates CTQ-SF scores. (B, D) Positive association demonstrating that elevated maternal overprotection significantly correlates with higher CTQ. Error bands and bars represent 95% confidence intervals.

Disclosures: E. Zaldívar Morales: None. **M. Flores-Ramos:** None. **I. Espinosa Méndez:** None. **T.V. Roman-Lopez:** None. **M.E. Rentería:** None. **A. Medina-Rivera:** None. **A.E. Ruiz-Contreras:** None. **S. Alcauter:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.02/E2

Topic: A.08. Adolescent Development

Support: R37MH080243

Title: Changes in Gray Matter Microstructure and Local Functional Connectivity Support Inhibitory Control from Adolescence to Adulthood

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Abstract: Adolescence is marked by behavioral improvements in inhibitory control along with brain maturational processes affecting function and structure of cortical circuitry. Recent evidence in rodents shows a developmental decrease of axonal local inputs in the prefrontal cortex, suggesting a weakening of local connectivity supporting circuit refinement and optimal behavior. Microstructural changes in gray matter via synaptic pruning may underlie this refinement, though it remains unknown what aspect of microstructure is driving the reduction of local inputs or how this unfolds *in vivo* in normative development to support mature cognitive functioning. 178 participants ages 10-26 (94F; 17.39±4.83yo) completed two runs of an EOG-monitored anti-saccade task, a developmentally-validated measure of inhibitory control. Participants then completed a 3T MRI scan involving a multi-shell diffusion weighted imaging acquisition, resting state fMRI, and structural (T1w, T2w) scans. We derived Neurite Density Index in gray matter using NODDI, local functional connectivity with Regional Homogeneity (ReHo), and intracortical myelin using T1/T2w ratio. Age-related analyses of MRI measures were examined using generalized additive models across a network of cortical and subcortical regions implicated in inhibitory control. Statistical models controlled for hemisphere and motion. Neurite Density Index significantly increased with age across all regions, as did T1w/T2w ratio, while local connectivity (ReHo) showed decreases across cortical regions. Greater neurite density in cortical regions was associated with more accurate anti-saccade performance and lower ReHo, with and without controlling for T1w/T2w ratio. This suggests that microstructural changes beyond myelination (e.g., neurite count, glia, etc.) may contribute to functional specialization and improved inhibitory control. Finally, an interaction between local connectivity and neurite density best predicted inhibitory control performance, such that the maturity of neurite density had the greatest effect when local connectivity was immature. Our results suggest that the coordinated maturation of gray matter microstructure and local functional connectivity may support the emergence of stable, adult-level inhibitory control. Further, we find that effects of neurite density reflect microstructural properties beyond myelination alone, suggesting another potential mechanism, such as microglia, that supports circuit reorganization and improved behavior.

Disclosures: V. Dionisos: None. **V. Sydnor:** None. **W. Foran:** None. **F.J. Calabro:** None. **B. Luna:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.03/E3

Topic: A.08. Adolescent Development

Title: Brain morphological patterns are associated with the presence, severity, and transitions of transdiagnostic psychiatric disorders in preadolescents

Authors: *N. KUANG[1], Y. YANG[2];
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Abstract: Cognitive function, psychological processes, mental states, and behaviors are key dimensions of human subjective experience that separately relate to mental disorders across diagnostic categories. However, whether these dimensions are linked to common or distinct brain morphological patterns that convey risk or resilience for psychiatric disorders remains unclear. The current study is a longitudinal investigation on 11,875 youths from the Adolescent Brain Cognitive Development (ABCD) Study aged 9-10 years at baseline. A machine learning approach based on canonical correlation analysis was used to identify latent dimensional associations of cortical morphology (4 metrics: surface area, cortical and subcortical volume, cortical thickness, and sulcal/gyral depth) with multidomain behavioral assessments including cognitive scores and psychological measures indexing motivation, impulse control, mental states, and behaviors across a normative continuum from healthy to pathological. Across morphological measures, we identified a robust latent brain structural variate that correlated positively with cognitive performance and negatively with psychological measures indexing greater psychopathology. Higher scores on this brain variate reflected larger cortical surface area and cortical volume, especially in temporal gyri, together with a posterior-anterior gradient in cortical thickness, showing greater thickness in occipital, parietal, and temporal cortices and lower thickness in cingulate and frontal regions. This brain variate and the related cognitive-psychological-behavioral variate remained stable at 2-year follow-up, demonstrating temporal consistency. The brain variate showed a dose-dependent relationship with the cumulative number of psychiatric diagnoses assessed concurrently and at 2-year follow-up, with lower scores associated with more comorbid diagnoses. In addition, baseline brain scores were associated with longitudinal transitions between healthy and diagnosed states over 2 years: lower scores predicted persistent psychiatric diagnoses, whereas higher scores predicted persistent healthy states, suggesting that this variate captures a vulnerability-resilience continuum for psychopathology. By revealing shared brain structural substrates across conventional diagnostic boundaries, these findings advance neurodevelopmental understanding of psychiatric disorders

and highlight the utility of morphology-informed approaches for early screening and intervention in youth.

Disclosures: N. kuang: None. **Y. Yang:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.04/E4

Topic: A.08. Adolescent Development

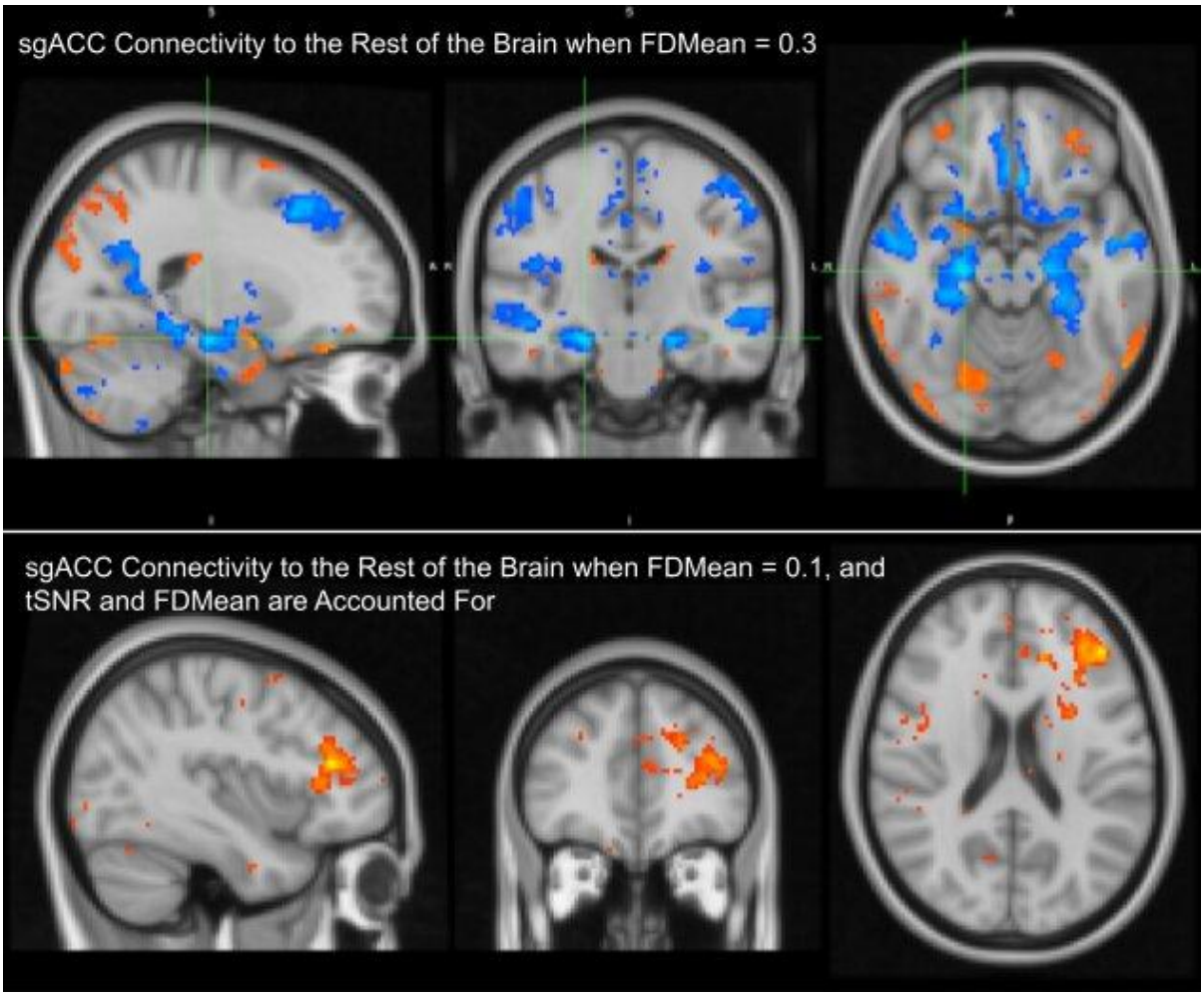
Support: Intramural Research Program ZIAMH002781; to D.S.P.

Title: Developmental Trajectories of sgACC Connectivity and Motion Thresholds

Authors: *J. LENTZ[1,2], E. GIAMPETRUZZI[4], D. M. NIELSON[3], D. S. PINE[2], F. PEREIRA[3], A. ZUGMAN[2];
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Abstract: Subgenual Anterior Cingulate Cortex (sgACC) connectivity to the dorsolateral Prefrontal Cortex (dlPFC) is linked to depression, but the sgACC is difficult to study as it is highly susceptible to signal dropout, causing low temporal signal to noise ratio (tSNR), which is exacerbated by motion. Our prior analysis showed that the sgACC's connectivity to the rest of the brain changes throughout adolescence, but including measures of in-scanner motion in the model made the finding no longer significant. Driven by this, we chose to test this model at two different motion thresholds during preprocessing steps. We hypothesized that the sgACC's seed-based functional connection to other regions would change throughout development in adolescence, but that this relationship would go away at the stricter motion threshold. In this work we use data from healthy human youth in the Adolescent Brain Cognitive Development (ABCD) study (n = 1051, 51% female, mAge = 10.93, age range 8-15, n scans = 1617). We preprocessed our fMRI data at two motion thresholds (Framewise Displacement (FD) = 0.1 and 0.3), then ran the following mixed effects model, where y is the connectivity of the sgACC for each scan: y ~ Age*Sex + 1 + (1|MRI Manufacturer/Collection Site) + (1|Family in ABCD). We also created an additional model including tSNR in the sgACC and FDmean as covariates. At the top of Figure 1, colored voxels show a significant change in connection with the sgACC by age after correction for multiple comparisons at the less strict motion threshold (blue = less connected over time, red = more). When computing the model with tSNR and FDmean at this threshold, this age effect is no longer significant. At the more stringent FD threshold (bottom of Figure 1) the age effect goes away for many regions, but remains significant in the left dlPFC even when tSNR and FDMean are included in the model. The results shown here have implications for current seedmap-based methods used in depression research, as age specific

seedmaps may be necessary due to the changing nature of sgACC to dlPFC connectivity, even at strict motion thresholds.



Disclosures: J. Lentz: None. **E. Giampetruzzi:** None. **D.M. Nielson:** None. **D.S. Pine:** None. **F. Pereira:** None. **A. Zugman:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.05/E5

Topic: A.08. Adolescent Development

Support: the Indian Council of Medical Research (ICMR), India (5/4-4/16/MH/2022-NCD-II)

by ICMR, India grant (ICMR/MRC-UK/3/M/2015-NCD-I)
Medical Research Council grant (MR/N000390/1)

Title: Age-dependent associations of plasma Glial Fibrillary Acidic Protein (GFAP) with externalizing psychopathology and atypical brain connectivity

Authors: *N. B S[1], B. HOLLA[2], S. SUBRAMANIAN[1], G. N[1], K. BHARGAVI[1], G. UDUPI[3], C. G K[1], S. MUCHUKUNTE MUKUNDA[4];
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Abstract: Externalizing disorders are common neurodevelopmental conditions, yet their underlying neurobiology remains incompletely understood. Integrating peripheral biomarkers with neuroimaging may provide valuable insights into the mechanisms underlying these disorders. This study investigated the associations of plasma biomarkers of glial activation (glial fibrillary acidic protein; GFAP) and axonal injury (neurofilament light chain; NfL) with functional brain connectivity and externalizing psychopathology (EXT) in a neurodevelopmental cohort.A cross-sectional study was conducted in 144 participants from the Indian Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA) cohort. Participants were balanced into EXT and healthy control (HC) groups using Mahalanobis distance matching. Plasma GFAP and NfL concentrations were quantified using single-molecule array (Simoa) technology. Resting-state functional MRI data were used to derive between-network connectivity deviation scores through normative modelling. Gamma generalized linear models (Gamma GLMs) assessed age-by-EXT interactions on biomarker levels, while sparse partial least squares (sPLS) regression identified connectivity features associated with biomarker concentrations.A significant age-by-EXT interaction was observed for GFAP ($p = 0.002$), indicating that EXT was associated with elevated GFAP levels in younger participants (<14 years), but not in older individuals. No significant effects were detected for NfL. The sPLS analysis identified a significant multivariate brain connectivity signature associated with GFAP levels, comprising five connectivity features. This pattern was characterized by increased connectivity between sensorimotor and limbic networks, increased connectivity between attention and default mode networks, and reduced within-network connectivity of the default mode network.These findings demonstrate an age-dependent association between elevated plasma GFAP levels and externalizing psychopathology, suggesting a potential role for glial activation in the early pathophysiology of these disorders. Furthermore, GFAP was linked to a distinct pattern of functional brain dysconnectivity, highlighting a potential neurobiological signature that may contribute to understanding the developmental mechanisms underlying externalizing disorders.

Disclosures: N. B s: None. **B. Holla:** None. **S. Subramanian:** None. **G. N:** None. **K. Bhargavi:** None. **G. Udupi:** None. **C. G k:** None. **S. Muchukunte Mukunda:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.06/E6

Topic: A.08. Adolescent Development

Title: Longitudinal Analysis of Sex Differences in White Matter Development across the Pubertal Transition in Typically-Developing Children

Authors: *A. CAMARA[1,3], S.-M. WEI[3], T. NASH[4], S. KIPPENHAN[2], P. J. SCHMIDT[5], K. F. BERMAN[6], T. TIAN[3], J. YANOVSKI[7];
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Abstract: Background: Puberty is a critical developmental period marked by substantial changes in cognition and behavior and increased psychiatric vulnerability. White matter microstructure continues to mature throughout puberty, paralleling cognitive and behavioral changes. Although sex differences in white matter development have been reported, many studies have not specifically examined pubertal development and have been limited by confounding factors such as cross-sectional designs or sparse temporal sampling during a period of rapid neurodevelopmental change, as well as high collinearity between age and pubertal stage. Here, we leveraged data from the "NIMH Intramural Longitudinal Study of the Endocrine and Neurobiological Events Accompanying Puberty" to characterize sex differences in how pubertal status relative to chronological age associates with white matter microstructure in healthy boys and girls, using longitudinal assessments spanning prepuberty through age 18.**Methods:** Diffusion Tensor Imaging MRI data were collected every nine months across 656 longitudinal visits from 142 typically developing children and adolescents (79 boys, 63 girls) aged 8-18 years (mean age 12.3±2.7). To isolate pubertal effects from chronological age, clinician-ascertained pubertal stage (PS) was residualized for age separately within sex using linear mixed-effects models. Residuals represented age-adjusted PS scores, where higher values indicated more advanced PS for age. Native-space fractional anisotropy (FA) maps were nonlinearly warped to a common template using FSL FNIRT and smoothed with a 2-mm FWHM Gaussian kernel. Voxelwise analyses were conducted and mapped within a white matter mask using AFNI's 3dMSS to test for sex differences in FA development with respect to age-adjusted PS, thresholded at pFDR < 0.05. **Results:** Sex differences were observed in several white matter tracts, including higher FA in boys than girls, within the bilateral anterior thalamic radiations, bilateral superior corona radiata, left cingulum bundle, and left cerebellar white matter. No interaction between sex and age-adjusted PS was observed. **Conclusion:** Using a temporally high-density longitudinal design spanning prepuberty through age 18, we identified robust sex differences in white matter microstructure across puberty, with boys exhibiting higher FA than girls in several major white matter tracts. The mechanisms underlying these sex differences remain unclear but may involve differential exposure to sex hormones during pubertal

maturation. Future studies will investigate the extent to which sex hormones contribute to these sex differences across puberty.

Disclosures: A. Camara: None. **S. Wei:** None. **T. Nash:** None. **S. Kippenhan:** None. **P.J. Schmidt:** None. **K.F. Berman:** None. **T. Tian:** None. **J. Yanovski:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.07/E7

Topic: A.08. Adolescent Development

Support: NIH Grant MH080243

Title: Dopaminergic maturation contributes to a developmental shift from exploration to task-optimal reward learning through adolescence

Authors: *F. J. CALABRO[1], A. PARR[2], B. LARSEN[4], B. LUNA[3];
[1]Psychiatry, [3]Dept. of Psychiatry, [2]Univ. of Pittsburgh, Pittsburgh, PA; [4]Univ. of Minnesota, Minneapolis, MN

Abstract: Heightened reward seeking is a hallmark of adolescence and is widely attributed, in part, to developmentally-specific changes in dopaminergic signaling. However, the mechanism by which these neurobiological changes shape adolescent-specific patterns of reward learning remain incompletely characterized. To address this, we examined reward learning within a multi-modal, 3T neuroimaging study of 145 youth aged 12-30 years with an accelerated longitudinal design (n=306 total visits). Participants completed a spatial reward learning task during fMRI acquisition, alongside MRI-based measures of striatal tissue iron which have been previously associated with dopamine (DA) availability. Using reinforcement learning (RL) models of task data, we identified a developmental transition from stochastic exploratory decision-making early in adolescence to increasingly reward exploitative strategies in young adulthood ($t=-2.49$, $p=0.013$). This shift occurred in conjunction with improved tuning of learning rates toward values that were optimal for maximizing reward outcomes given the task environment. Developmental changes in RL parameters were associated with age-related increases in ventral striatal (Nucleus Accumbens) tissue iron ($t=-3.20$, $p=0.0017$), suggesting that maturational changes in dopaminergic neurophysiology may support heightened exploratory decisions in adolescence, as well as the transition to the use of task-optimal learning strategies into adulthood. RL parameters were further linked with fMRI-based reward-related activation in ventromedial prefrontal and posterior parietal cortices (cluster-corrected $p_{FWE}<0.05$). Notably, these regions tracked choice patterns differentially across age, exhibiting preferential responses to exploratory strategies in adolescence, but favoring task optimal learning strategies in adulthood. Together, these results support a model by which the developmental shift from exploration-dominant

decision-making during adolescence to cortically-mediated, strategically optimized reward learning in adulthood is supported by the maturation of the striatal dopamine system.

Disclosures: F.J. Calabro: None. **A. Parr:** None. **B. Larsen:** None. **B. Luna:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.08/E8

Topic: A.08. Adolescent Development

Support: NIH Grant UL1TR001857
NIMH MH067924
University of Pittsburgh Clinical and Translational Science Institute (CTSI)
Department of Bioengineering
Staunton Farm Foundation

Title: Developmental Shifts in Hippocampal Excitation-Inhibition Balance Parallel HPC-vmPFC Connectivity and the Emergence of Goal-Directed Behavior Across Adolescence

Authors: *D. S. WRIGHT[1], D. J. PETRIE[2], V. J. SYDNOR[3], O. RAVINDRANATH[8], A. C. PARR[4], W. FORAN[5], F. J. CALABRO[6], B. LUNA[7];
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Abstract: Adolescence is marked by increased long-term goal pursuit, supported by the protracted maturation of circuits that integrate prior experiences for flexible adaptation. Maturational increases in hippocampal (HPC)-ventromedial prefrontal cortex (vmPFC) coupling parallel developmental improvements in context-dependent decision-making. Although structural and functional HPC development have been studied, the neuroplastic mechanisms that support this maturation remain underexplored. Prior work shows adolescent changes in PFC excitation-inhibition (E/I) balance reflecting ongoing plasticity, yet similar refinements in the HPC—and how they contribute to HPC-vmPFC functional integration—remain unclear.Using 7T MRSI and resting-state fMRI, we characterized developmental trajectories of excitatory (glutamate, Glu) and inhibitory (GABA) concentrations and subregion-to-vmPFC functional connectivity along the HPC longitudinal axis (head, body, tail) and their associations with goal-directed behavior in 124 participants aged 10-32 years (177 visits; up to 3 each). Goal-directed behavior was indexed using a two-stage sequential decision-making task characterizing model-based and model-free learning strategies and learning rates. Multilevel modeling tested nonlinear relationships among age, neurochemistry, connectivity, and behavior.Consistent with prior PFC findings, HPC Glu declined with age across all subregions ($p < .009$), whereas GABA showed no significant age-

related changes. HPC E/I—indexed by regressing Glu onto GABA—became significantly more balanced with age, particularly in the HPC tail ($p < .001$). In parallel, age-related increases in HPC-vmPFC connectivity emerged in the body and tail ($p < .001$), with HPC E/I balance moderating the relationship between age and HPC-vmPFC connectivity in the HPC body ($p < .05$). HPC-vmPFC connectivity patterns were further related to adult-like decision-making: body and tail-vmPFC connectivity predicted model-based behavior ($p < .001$), while head-vmPFC connectivity predicted second-stage learning rate ($p = .004$) and model-free behavior ($p < .001$).These results suggest that refinements of excitatory signaling in the HPC facilitate age-related increases in HPC-vmPFC coupling, supporting model-based behavior. Subregion specificity—posterior areas (body, tail) showing stronger E/I shifts linked to model-based behavior; anterior areas (head) more associated with learning rate and model-free behavior—may reflect functionally distinct roles along the longitudinal axis undergoing unique neurodevelopmental trajectories.

Disclosures: D.S. Wright: None. **D.J. Petrie:** None. **V.J. Sydnor:** None. **O. Ravindranath:** None. **A.C. Parr:** None. **W. Foran:** None. **F.J. Calabro:** None. **B. Luna:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.09/F1

Topic: A.08. Adolescent Development

Support: U01DA041117
U24DA041123
U24DA041147

Title: Adolescent Substance Use, Multilevel Risk, and Neurocognitive Development in the ABCD Study

Authors: P. J. RODRIGUEZ RIVERA[1], *C. C. CLOAK[1], L. SHICHMAN[1], T. ERNST[1], L. CHANG[1,2];
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Abstract: Background: Early adolescent substance use (ASU) is linked to psychosocial and neurodevelopmental vulnerability, yet the developmental correlates of substance-use occurrence and escalation remain poorly understood. Furthermore, most studies do not distinguish between occurrence and escalation, two related but potentially distinct processes that may be influenced by different risk factors and developmental mechanisms. We examined longitudinal associations among multidomain psychosocial risk, ASU occurrence and escalation, and cognitive and cortical development during adolescence. **Methods:** Data were drawn from the Adolescent Brain Cognitive Development (ABCD) Study (baseline-Year 7). Psychosocial domains were derived using confirmatory factor analysis. ASU occurrence and escalation were estimated using two-

part longitudinal models across ages 9-17 and incorporated into mixed-effects models of cognitive performance and cortical thickness, surface area, and volume, adjusting for psychosocial, demographic, and imaging covariates, with random intercepts for participant and scanner. **Results:** Factor analysis supported a four-domain structure (familial substance-use liability, socioeconomic adversity, behavioral dysregulation, and reward sensitivity; RMSEA=0.04). Family substance-use liability emerged as the strongest and most consistent predictor of ASU occurrence and escalation, with associations strengthening across adolescence (all FDR-$p<0.001$), whereas socioeconomic adversity and reward sensitivity demonstrated more selective associations, particularly with marijuana occurrence and escalation (all FDR-$p<0.01$). Greater ASU occurrence and escalation were associated with lower processing speed, episodic memory, and inhibitory control scores over time (all FDR-$p<0.05$). Higher ASU occurrence was associated with smaller superior frontal and temporal cortical surface area and volume (all FDR-$p<0.05$), whereas escalation was associated with broader reductions in cortical volume trajectories, particularly within superior frontal, caudal middle frontal, and superior temporal regions (all FDR-$p<0.05$). **Conclusions:** Familial substance-use liability emerged as a key risk factor for adolescent substance use. Greater ASU occurrence and escalation were associated with poorer cognitive performance and reduced cortical surface area and volume, with escalation explaining additional variance beyond occurrence for select cognitive and cortical outcomes. Distinguishing occurrence from escalation may improve understanding of neurodevelopmental pathways underlying adolescent substance use.

Disclosures: P.J. Rodriguez Rivera: None. **C.C. Cloak:** None. **L. Shichman:** None. **T. Ernst:** None. **L. Chang:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.10/F2

Topic: A.08. Adolescent Development

Support: NIDA Grant K01DA053438

Title: Real-world positive affect states, behaviors, and midbrain dopamine system function across adolescence

Authors: *C. WANG[1,2], D. V. CLEWETT[3], A. O. COHEN[2];
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[3]Psychology, UCLA, Los Angeles, CA

Abstract: Adolescence is a transitional developmental period marked by changes in reward processing and motivated behaviors. The mesolimbic dopamine (DA) system undergoes significant changes across adolescence, which have been linked to shifts in reward-related behaviors, like substance use, and in positive affect. However, investigation of DA system

function over development has been limited by a dearth of youth friendly methods. Neuromelanin (NM), a by-product of catecholamine metabolism, accumulates over time and can be detected by neuromelanin sensitive MRI (NM-MRI). Its signal intensity in the substantia nigra (SN) and ventral tegmental area (VTA) is increasingly used as a proxy for DA system function in both healthy and clinical populations. Existing research on DA system function using NM-MRI has mostly linked NM MRI signal to static measures of clinical diagnosis or affect, like questionnaires done in lab visits. Whether these findings generalize to affective dynamics in the real world remains an important question. This study aimed to examine associations between NM-MRI signals in midbrain DA regions and real-world affective states across development. Ecological Momentary Assessment (EMA) surveys were administered outside of the laboratory to examine how fluctuations in real-world positive affect vary across the childhood and early adolescence. We then examined whether these EMA measures, including substance use, were related to NM-MRI signal in the DA system across age. Participants aged 10-25 completed one NM-MRI scan during a lab visit. They then provided subjective affect ratings and reported substance use every two days for five months. We found that higher average levels of real-word positive affect across the five months was negatively correlated with age and substance use was positively correlated with age. By contrast, no relationship was observed between age and measures of the temporal variability in affective ratings. While greater substance use behavior and age, but not positive affect, each positively predicted NM-MRI signal, the relationship with substance use disappeared after controlling for age. These results suggest that real-world substance use may relate to DA system function across age, but that age is ultimately a stronger predictor of dopamine system NM-MRI signal.

Disclosures: C. Wang: None. **D.V. Clewett:** None. **A.O. Cohen:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.11/F3

Topic: A.08. Adolescent Development

Support: F31DA060068
U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01

Title: Unsupervised machine learning to identify subcortical brain subtypes in adolescents with persistent distressing psychotic-like experiences

Authors: *D. NGUYEN[1,2], C. AMIR[1], C. E. BEARDEN[3,1];
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Abstract: Childhood psychotic-like experiences (PLEs) are associated with a range of adverse outcomes, including later onset of psychotic disorders; yet, risk profiles and developmental patterns have not been fully investigated. While abnormalities in the hippocampus (HPC) and ventral striatum (VS) have been documented in psychosis-risk populations, studies have focused on functional connectivity rather than the combined growth trajectories of these regions. This study aimed to investigate whether neurobiologically distinct subgroups defined by HPC and VS growth trajectories exist among adolescents with PLEs. Participants included 6,335 adolescents (47.4% female) from the Adolescent Brain Cognitive Development (ABCD) Study, classified as either non-PLE (n =5,910, 46.4% female) and PLE-positive (n = 425, 60.9% female). The PLE-positive group was defined as having Prodromal Questionnaire-Brief Child Version (PQ-BC) distress scores >1.96 *SD* above the mean at two or more assessments, consistent with prior ABCD studies. Baseline values and growth rates for subcortical volume measured by structural MRI for the HPC and VS were estimated using Best Linear Unbiased Predictors (BLUPs) from linear mixed-effects models adjusted for age, sex, study site, and family structure, spanning six years beginning when participants were aged 9-to-11. Using these estimates, hierarchical cluster analysis of PLE-positive participants identified three distinct neurodevelopmental subgroups with a silhouette score of 0.17 and an Adjusted Rand Index of 0.36 across 10,000 bootstrap iterations. Relative to the non-PLE group baseline volumes (HPC: M = 8740.19 mm³; VS: M = 1459.28 mm³) and growth trajectories, Group A (n = 104) was characterized by high baseline volumes (HPC: M = 9085.63 mm³; VS: M = 1643.52 mm³) and flat growth rates in both regions. Group B (n = 222) showed lower baseline volumes (HPC: M = 8221.19 mm³; VS: M = 1387.01 mm³) with relatively steeper growth trajectories in both regions. Group C (n = 99) exhibited elevated hippocampal baseline volume (HPC: M = 9413.43 mm³) with flat growth slopes, alongside normative striatal baseline volume (VS: M = 1461.70 mm³) and growth. Although symptom frequencies overlapped across groups, each subgroup showed a relative predominance of specific clinical features: disorganized speech in Group A, grandiose ideation in Group B, and distress associated with paranoia and derealization in Group C. Overall, results indicate heterogeneity in neurodevelopment and symptomatic profiles within PLE-positive adolescents, warranting longitudinal follow-up to determine which of these subtypes carry risk for later overt psychotic disorder.

Disclosures: D. Nguyen: None. **C. Amir:** None. **C.E. Bearden:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.12/F4

Topic: A.08. Adolescent Development

Support: NSF Grant 2207733

Title: Intrinsic BOLD Oscillations in the Developing Adolescent Brain Support Cognitive Processing Across Domains

Authors: M. MANJUNATH[1], ***C. STAMOULIS**[2,1];
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Abstract: Intrinsic brain oscillations play a critical role in cognitive function, but the spatio-spectral characteristics, structural underpinnings and cognitive correlates of infra-slow (<0.5 Hz) BOLD oscillations in the developing adolescent brain are poorly understood. In n=3507 youth (median(IQR) age =12.0(1.1) years; 50.9%-females) from the Adolescent Brain Cognitive Study, intrinsic oscillations were estimated from resting-state fMRI signals, using an unsupervised time-domain method. Mixed-effects regression models tested their associations with participant characteristics, regional morphometric properties and cognitive measures. Four intrinsic oscillations were estimated in the range 0.02-0.04, 0.04-0.08, 0.08-0.10 and 0.10-0.15 Hz, with highest amplitudes in posterior (primarily visual) followed by prefrontal areas, and lowest amplitudes in somatomotor regions. Older youth and/or in later pubertal stages had lower oscillation amplitudes in temporal regions and orbitofrontal cortex at higher frequencies (β=-0.15 to -0.03, 95%CI = [-0.20, -0.01]), and higher oscillation amplitudes in prefrontal regions (β=0.01-0.20, 95%CI=[0.01,0.33]). At frequencies ≥0.10 Hz, higher cortical thickness and/or myelin were associated with higher oscillation amplitudes in superior frontal, posterior cingulate, primary visual and and temporal regions (β=0.03-0.06, 95%CI = [0.01, 0.10]). At lower frequencies, higher cortical thickness and/or myelin were associated with lower oscillations in inferior parietal, transverse temporal, and superior temporal regions and the isthmus of the cingulate gyrus (β=-0.07 to -0.04, 95%CI = [-0.13, -0.01]. Across distributed brain regions, higher oscillation amplitudes at frequencies ≥0.08 Hz were associated with better performance in tasks assessing inhibitory control and cognitive flexibility, visuospatial processing, attention, language comprehension, reading, and memory (β=0.04-0.10, 95%CI=[0.01,0.18]). Intrinsic BOLD oscillations are measurable in the adolescent brain, have specific spatial patterns, are correlated with the brain's underlying morphology, and play ubiquitous roles in cognitive processing.

Disclosures: M. Manjunath: None. **C. Stamoulis:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.13/F5

Topic: A.08. Adolescent Development

Support: NIH Grant R01MH130899

Title: Longitudinal Individualized Functional Parcellation Reveals Dynamic Network Boundary Shifts in Adolescent Depression

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Abstract: Major depressive disorder (MDD) is a prevalent adolescent condition characterized by marked clinical heterogeneity. Identifying neurobiological markers during this critical developmental window (ages 9-17) requires precision functional mapping (PFM) to delineate individual-specific brain topography and accurately capture the neural substrates underpinning MDD.
However, a critical gap remains in characterizing longitudinal brain network changes for individual adolescents. Previous studies overwhelmingly rely on resting-state fMRI and static, group-averaged atlases. This conventional approach obscures subject-specific variations in functional topography across cognitive states and development, leaving it unknown how personalized, dynamic network shifts correlate with MDD onset, persistence, and remission trajectories.
To address this, we applied a hierarchical Bayesian parcellation (HBP) framework that integrates both task-based and resting-state fMRI to generate dynamic, individualized cortical parcellations. We constructed a longitudinal cohort utilizing the Adolescent Brain Cognitive Development (ABCD Release 7.0) dataset. This yielded a curated sample of N=1,080 adolescents (ages 9-11 at baseline) who possess continuous, high-quality neuroimaging and comprehensive behavioral phenotype data spanning up to a 7-year follow-up. By systematically harmonizing multi-visit task and resting-state data, our HBP model precisely delineates subject-specific network boundaries at each distinct developmental timepoint. We hypothesize that these dynamically updated, multimodal parcellations will reveal novel MDD-related alterations and provide greater prognostic value than static or rest-only group features.
Preliminary results show that our fused task-and-rest individualized parcellations achieve higher intra-subject reliability versus rest-only models. Having successfully derived these individual longitudinal parcellations, our ongoing analyses focus on quantifying major functional network boundary shifts across the developmental window. Using linear mixed-effects models, we will examine how these personalized, time-varying alterations in spatial network topography and functional connectivity directly relate to individualized MDD symptom trajectories. We expect that evaluating these longitudinal spatial shifts alongside baseline clinical phenotypes will significantly enhance the prediction of future depression severity, underscoring the necessity of dynamic, individualized mapping in adolescent mental health.

Disclosures: D. Zhi: None. **T. Ge:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.14/F6

Topic: A.08. Adolescent Development

Support: NIMH Grant MH067924
NIH Grant UL1TR001857

Title: Developmental interactions between oscillatory and spontaneous neural activity support improvements in inhibitory control from adolescence into adulthood

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Abstract: Adolescence is a critical period of development marked by improvements in inhibitory control—the ability to suppress a prepotent response in favor of a goal-directed one. Neural mechanisms supporting inhibitory control mature into adulthood, enabling more accurate and reliable performance on response inhibition tasks, such as the anti-saccade (AS) oculomotor task. Frequency-specific neural oscillations during AS response preparation are crucial for correct responses, with developmental refinements in oscillatory activity contributing to improved performance. Prior work has established that developmental refinements in neural circuitry support decreases in spontaneous activity, stabilizing cognitive performance. However, the interplay between oscillatory and spontaneous activity during task in supporting developmental improvements in inhibitory control remains poorly understood. We show that broadband spontaneous preparatory activity decreased with age in both tasks ($p<0.001$), with a significant age-by-condition interaction ($p=0.001$) where adolescents showed greater suppression of spontaneous activity during AS than adults, relative to VGS. Decreases in spontaneous power were associated with improved performance ($p=0.03$) and reduced latency variability ($p=0.01$). Five preparatory ERSP clusters showed age-by-condition interactions: three gamma-band clusters (40-43, 44-50, and 49-70 Hz), a low-beta cluster (24-28 Hz), and a high-beta cluster (30-32 Hz). Of these, increased mid-gamma activity (44-50 Hz) was associated with improved AS performance ($p=0.003$) and reduced variability ($p=0.003$), while decreased high-beta activity was related to reduced latency variability ($p=0.005$) and reduced spontaneous activity, most pronounced in adults ($p=0.009$). While spontaneous activity supports flexible circuitry, during task it may represent a neural "noise floor", impeding inhibitory control by priming reflexive responses. Age-related increases in gamma band activity may signal core aspects of task performance, reflecting task-evoked activity rather than spontaneous activity. In contrast, high-beta development may reflect prefrontal circuit maturation that reduces spontaneous activity. Adolescents showed greater high-beta modulation during AS from VGS, suggesting their circuits are less readily primed for cognitive tasks, requiring greater high-beta modulation to overcome spontaneous activity. These results provide new evidence for the mechanism underlying stabilization of cognitive control performance via maturation of spontaneous and oscillatory neural activity.

Disclosures: A.M. Beatty: None. **S. McKeon:** None. **D.J. Petrie:** None. **F.J. Calabro:** None. **A.C. Parr:** None. **B. Luna:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.15/F7

Topic: A.08. Adolescent Development

Support: NIAAA Grant K01AA030610
NIAAA Grant U10AA008401

Title: Exploring cognitive mechanisms linking parental bonding and alcohol use disorder in adolescence and young adulthood

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Abstract: Alcohol use disorder (AUD) is characterized by neurocognitive disinhibition. Individuals with AUD and their children often manifest lower EEG activity on measures of quantifiable brain responses (e.g., frontal theta oscillations) indicating impaired self-regulation and executive functioning. Further, cognitive biases and deficits may also contribute to the development and maintenance of AUD. Particularly, cognitive biases such as alcohol expectancies or beliefs about the cognitive, social, and behavioral impacts of alcohol are shown to begin in childhood and adolescence and predict alcohol use initiation and drinking patterns over time. Past work has shown that even among adolescents with high-risk for developing AUD, closeness with parents is associated with less problematic drinking and healthier neurocognitive development. Extending this work, we examined the association between parental bonding and alcohol use problems in adolescence and young adulthood with a focus on understanding the cognitive mechanisms between them. We focused on two cognitive aspects: positive alcohol expectancies and neural response inhibition. Data from the Prospective study (N=3,527, M_{age}=16.10, Females=51%) of the Collaborative Study on the Genetics of Alcoholism were used. Using a parallel mediation path model, we examined the direct association of mother- and father-bonding with age of onset of regular drinking and DSM-5 AUD symptoms in offspring and the indirect associations between them via positive alcohol expectancies and neural response inhibition. Positive alcohol expectancies were assessed using the Alcohol Expectancy Questionnaire (AEQ) and the neural response inhibition was represented by frontal theta power, an EEG brain activity, recorded during a Go/No-Go task. The models were adjusted for self-reported sex, race/ethnicity, and parental AUD status. We found that greater mother- and father-bonding were associated with fewer AUD symptoms and later age of onset of regular drinking. We also found that both mother- and father-bonding were indirectly associated with fewer AUD symptoms and later onset of regular drinking via lower positive alcohol expectancies. Interestingly, greater father (not mother)-bonding had a significant indirect associated with fewer AUD symptoms via enhanced response inhibition. This work underscores parental bonding as a protective factor and provides evidence for the cognitive
mechanisms through which response inhibition and alcohol expectancies can mediate the interplay between parental-bonding and alcohol use and problems in offspring.

Disclosures: G. Pandey: None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.16/F8

Topic: A.06. Developmental Disorders

Support: NIH/CATS KL2TR000446 (PI: Woynaroski)
NIH/NIDCD R21DC016144 (PI: Woynaroski)
NIH/NIDCD R01DC020186 (PI: Woynaroski)
F31DC023783 (PI: Pulliam)
NSF NRT grant DGE 19-22697 (PI: Wallace)
NSF NRT grant 19-22697
Asness Family Fund (PI: Stassun; training support for Pulliam)

Title: Differences in Decreased Sound Tolerance and Links with Auditory Function (or Lack Thereof) in Children with High and Low Familial Likelihood for Autism

Authors: *R. G. GORDON[1], G. T. PULLIAM[4], J. I. FELDMAN[5], S. CLARK[2], T. G. WOYNAROSKI[3];
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Abstract: **Motivation:** Autism is a neurodevelopmental condition characterized by differences in social communication, the presence of restricted and repetitive behaviors, and sensory features. Among the sensory features associated with autism, decreased sound tolerance (DST) is particularly prevalent, persistent, and disabling. The younger siblings of autistic children (Sibs-Autism) are at increased familial likelihood for autism, and thus hypothetically for DST, relative to the younger siblings of non-autistic children (Sibs-NA).**Purpose:** This study aims to test whether there are differences in DST, specifically hyperacusis and misophonia symptoms, and associated auditory system differences in Sibs-Autism and Sibs-NA in early childhood.**Methods:** Sixty participants (30 Sibs-Autism, 30 Sibs-NA) from an NIH-funded project are being recruited for this supplemental study funded by the Misophonia Research Fund. At 5-8 years, hyperacusis symptoms are measured via the Pediatric Hyperacusis Questionnaire, and misophonia symptoms are measured via the Parent-Report Misophonia Assessment Questionnaire. Concurrently, a comprehensive audiological assessment, including tympanometry, pure tone audiometry, acoustic reflex testing, transient-evoked otoacoustic emissions, and auditory brainstem responses is completed. Diagnostic status is ascertained by the Autism Diagnostic Observation Schedule and clinical interview.**Results:** Preliminary analyses were run on data collected and verified to date (for 15 Sibs-Autism and 14 Sibs-NA, matched on age and sex). MANOVA revealed a large effect of group, $F(4,52) = 4.053$; $p = .006$, $\eta_p^2 = .238$. Post hoc tests showed that Sibs-Autism

who received an autism diagnosis (Sibs-Autism-dx) had significantly greater hyperacusis and misophonia symptoms relative to Sibs-Autism who did not receive a diagnosis (Sibs-Autism-nodx) and Sibs-NA (p values < .05). Hyperacusis symptoms were, further, strongly and positively correlated with misophonia symptoms ($r = 0.693$, $p < .001$). However, none of the putative predictors derived from the clinically standard audiological assessment were significantly associated with hyperacusis or misophonia symptoms after correcting for multiple comparisons.**Conclusions:** Preliminary results suggest that Sibs-Autism, specifically Sibs-Autism-dx, display DST by 5-8 years old. There is a high co-occurrence of misophonia and hyperacusis symptoms but limited evidence that alterations within the auditory system explain sound intolerance. Implications for research and clinical practice for children at high likelihood for neurodevelopmental communication disorders will be discussed.

Disclosures: R.G. Gordon: None. **G.T. Pulliam:** A. Employment/Salary (full or part-time):; Full-Time student. **J.I. Feldman:** A. Employment/Salary (full or part-time):; Full-Time Employee. **S. Clark:** A. Employment/Salary (full or part-time):; Employee Full-time. **T.G. Woynaroski:** A. Employment/Salary (full or part-time):; Full-Time.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.17/G1

Topic: E.06. Vision

Support: Support R01MH134004
R01NS120954

Title: Tract-level lateralization in language networks of the developing brains

Authors: S. VENKADESH[1], F.-C. YEH[2], P. R. HOF[3], ***J. R. KORENBERG**[4];
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Abstract: Hemispheric lateralization is a hallmark of the language network, yet the organization, age-related change, and cognitive relevance of its structural-connectivity asymmetry remain unclear. In the ABCD Study (baseline N~9,700, ages 9-11; 4-year follow-up ~4,500) we computed dMRI tract-to-region connectivity (DSI Studio) between five bilateral cortical regions (Heschl's gyrus, HG; planum temporale, PT; supramarginal, SMG; angular, AG; Broca's area, BA44) and major association tracts, derived a lateralization index (LI) per tract-region cell, and related LI to the NIH Toolbox battery by OLS with a discovery/validation split.First, the connectome shows a robust, regionally specific asymmetry landscape, all 24 cells were significantly lateralized (Wilcoxon, FDR<.05), 13 left- and 11 right-dominant, 17 with |LI|>=0.20. Asymmetry was tract- and region-specific, not global: the arcuate (AF) was left-

dominant at BA44 and PT but strongly right-dominant at AG (-0.88).Second, the landscape was stable across the sampled window (~9-15 y): the mean-LI pattern was essentially unchanged between baseline and the 4-years (cross-cell r=0.998), with moderate-high test-retest reliability (r~0.5-0.8).Third, LI predicted cognition in a region- and tract-specific, bidirectional manner. Effects were modest (partial r~0.03-0.06).Thus, connectivity asymmetry forms a regionally organized landscape, stable from late childhood into mid-adolescence, that couples to cognition region-specifically.

Disclosures: S. Venkadesh: None. **F. Yeh:** None. **P.R. Hof:** None. **J.R. Korenberg:** None.

Poster

PSTR212: Adolescent Development: Human Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR212.18/G2

Topic: A.08. Adolescent Development

Support: National Research, Development and Innovation Office of Hungary, Grant K-134370 to I.K.
Hungarian Research Network (HUN-REN-ELTE-PPKE Adolescent Development Research Group)
Faculty of Humanities and Social Sciences, Pázmány Péter Catholic University, PPKE-BTK-KUT-23-1
MICIU/AEI/10.13039/ 501100011033, PID2022-136216NB-I00 to G.D.
EU ERC Synergy Horizon Europe, ERDF, EU, Project NEurological MEchanismS of Injury, and Sleep-like cellular dynamics (NEMESIS) (ref. 101071900) to G.D.
Department of Research and Universities of the Generalitat of Catalunya, AGAUR research support grant (ref. 2021 SGR 00917) to G.D.
Centre for Eudaimonia and Human Flourishing (funded by the Pettit, Carlsberg and Cillo Foundations) to M.L.K.
Center for Music in the Brain (funded by the Danish National Research Foundation, DNRF117, The Lundbeck Foundation R469-2024-1573 and Købmand Herman Sallings Fond) to M.L.K.

Title: Pubertal timing defines distinct trajectories of adolescent brain development

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Abstract: Adolescence is a period of prolonged neuroplasticity across the cortex, a feature that supports continued experience-dependent refinement while also increasing vulnerability. While emerging evidence indicates that puberty shapes cortical development in the adolescent brain, how pubertal timing modifies developmental trajectories and periods of heightened vulnerability remains unknown. Here, we examine how pubertal timing shapes hierarchical cortical organization across adolescence and emerging adulthood, and influences vulnerability to sustained environmental disruption.

We utilize a cross-sectional dataset (N=61) and a longitudinal cohort of female participants assessed before (T1: N=87, 11.5-16 years) and after (T2: N=56, 17-20 years) the COVID-19 pandemic. Pubertal timing is defined as the difference between biological age (BA; measured via ultrasonic bone age assessments) and chronological age (CA) in adolescence. Participants are classified into accelerated, average, and decelerated pubertal maturity groups based on BA-CA discrepancy. Hierarchical cortical organization is quantified via HD-EEG-derived entropy production, an objective measure of brain function linked to both neuropsychiatric status and cognitive performance.

Group comparisons reveal reduced entropy production in both accelerated and decelerated groups in adolescence, indicating that hierarchical organization is best supported by an average pubertal timing. However, trajectory-based analyses reveal maturity group-specific developmental paths. The accelerated group shows attenuated neurodevelopment and persistently low hierarchical organization but no pandemic-related effect. The decelerated group exhibits rapid development and only a transient reduction in hierarchical organization, but also the strongest pandemic-linked disruption.

Our findings indicate that accelerated pubertal timing is associated with persistent disadvantage in hierarchical brain development, and periods of peak neurodevelopmental change define windows of heightened vulnerability to environmental disruption. Overall, our results support that variability in pubertal timing is not merely a collateral feature of adolescence but a fundamental influence in human neurodevelopment.

Disclosures: M. Szakács: None. **F. Gombos:** None. **M.L. Kringelbach:** None. **G. Deco:** None. **I. Kovács:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.01/G3

Topic: B.03. Ion Channels

Support: NIH grant DC01919 to LKK
NS139960 to LKK

Title: Membrane potential regulates filopodial extension and growth cone navigation by coupling Kv3.4 channels to the adhesion molecule Pcdh9

Authors: ***Y. ZHANG**[1], Z. SHAH[2], R. A. APONTE RIVERA[3], J. WU[2], H. WANG[4], L. K. KACZMAREK[1];
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Abstract: The Kv3.4 potassium channel is required for normal neuronal outgrowth. Loss of Kv3.4 results in impaired axonal elongation, errors of migration and pathfinding. The cellular and molecular mechanisms of this requirement, however, remain elusive. Using Yeast two hybridization and co-immunoprecipitation techniques, we found that the cytoplasmic C-terminal domain of Kv3.4 directly binds Protocadherin 9 (Pcdh9), a Ca^{2+}-dependent cell adhesion molecule that activates the WAVE actin-nucleating complex. This interaction is essential for normal Kv3.4 expression and, in the absence of Pcdh9, Kv3.4 subunits are degraded. Introduction of Kv3.4 into CHO cells stimulates Pcdh9-dependent formation of filopodia and this is dependent on membrane potential but not on ion flux through the channel. Depolarizations that promote channel opening stimulate filopodial extension while inactivation causes retraction. Neurite outgrowth is impaired in cerebellar granule cells from Kv3.4$^{-/-}$ mice and rescued by a non-conducting Kv3.4 mutant. Outgrowth depends on Kv3.4-dependent binding of Pcdh9 to the WAVE complex and is selectively disrupted by inhibiting this interaction. Furthermore, we tested the ability of the neurites of cerebellar granule neurons to navigate in a gradient of BDNF. While control neurons extended their neurites in the direction of the source of BDNF, neurons from Kv3.4$^{-/-}$ mice failed to respond to the gradient. Our findings reveal that the voltage-dependent, non-conducting function of potassium channel can directly couple membrane potential to cytoskeletal remodeling, establishing a novel mechanism where the channel acts as a voltage-dependent scaffold independent of ion permeation.

Disclosures: Y. Zhang: None. **Z. Shah:** None. **R.A. Aponte Rivera:** None. **J. Wu:** None. **H. Wang:** None. **L.K. Kaczmarek:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.02/G4

Topic: B.03. Ion Channels

Title: Acute Cocaine Exposure Upregulates Kcnj4 Expression in the Mouse Striatum: Integrated Transcriptomic and Proteomic Analyses

Authors: E. YU, E. CHAI, C. CACOULIDIS, A. KAPOOR, E. CHEN, G. BRADY, ***X. CHU**; Biomed. Sci., Univ. of Missouri Kansas City, Kansas City, MO

Abstract: Cocaine use disorder (CUD) is associated with persistent neuroadaptations within brain reward circuits; however, the molecular mechanisms underlying cocaine-induced plasticity remain incompletely understood. To identify genes and proteins responsive to acute cocaine exposure, we performed integrated transcriptomic and proteomic analyses of the striatum, a key region involved in reward processing and addiction-related behaviors. Adult wild-type mice received a single intraperitoneal injection of saline or cocaine (20 mg/kg). Striatal tissue was collected 24 h later for transcriptomic and proteomic profiling. Differentially expressed genes and proteins were analyzed to identify molecular targets altered by acute cocaine administration. Among the significantly regulated targets, Potassium Inwardly Rectifying Channel Subfamily J Member 4 (Kcnj4), which encodes the G protein-gated inwardly rectifying potassium (GIRK4) channel, was consistently increased at both the transcript and protein levels. Transcriptomic analysis revealed significant upregulation of Kcnj4 mRNA in cocaine-treated mice compared with saline controls (Q = 0.0052; n=3). Proteomic analysis similarly demonstrated increased Kcnj4 protein expression (fold change = 1.58, Q = 0.048; n=3). The concordant elevation of Kcnj4 transcript and protein levels suggests coordinated regulation following acute cocaine exposure. GIRK channels are important regulators of neuronal excitability and neurotransmission and have been implicated in reward-related signaling pathways. Our findings identify Kcnj4 as a cocaine-responsive target in the striatum and provide evidence for coordinated transcriptomic and proteomic adaptations induced by acute cocaine exposure. These results suggest that GIRK4-associated signaling may contribute to early molecular responses to cocaine and warrant further investigation in addiction-related behaviors.

Disclosures: E. Yu: None. **E. Chai:** None. **C. Cacoulidis:** None. **A. Kapoor:** None. **E. Chen:** None. **G. Brady:** None. **X. Chu:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.03/H1

Topic: B.03. Ion Channels

Support: NIH grant NS102239

Title: Slack (KCNT1) potassium channels remodel and regulate mitochondria of neurons

Authors: *H. WANG[1], Y. ZHANG[3], J. WU[2], E. A. JONAS[4], L. K. KACZMAREK[5]; [2]Pharmacol., [1]Yale Univ., New Haven, CT; [3]Pharmacol., Yale Univ. Sch. Med., New Haven, CT; [4]Yale Univ. Sch. Med., Hamden, CT; [5]Yale Univ. Sch. Med., New Haven, CT

Abstract: The Slack channel (KCNT1, KNa1.1) is a sodium-activated potassium channel expressed in neurons of the cerebral cortex, as well as in multiple other brain regions, where gain-of-function mutations cause several forms of childhood epilepsy and intellectual disability. Slack regulates synaptic plasticity, and its cytoplasmic C-terminus interacts with mRNA

translation machinery, including FMRP and CYFIP1, to modulate local protein synthesis. Here, we report a novel role for Slack in mitochondrial bioenergetics and cristae morphogenesis. By western immunoblotting, we have found that levels of the cristae-regulating proteins MIC60 and OPA1, as well as other inner mitochondrial membrane proteins are elevated, in the cerebral cortex of Slack knockout (KO) mice and of mice bearing the Slack-R455H gain-of-function mutation, relative to those in wild type mice. This result is consistent with proteomic analysis of cortices of both strains. Strikingly, visual inspection and quantitative analysis of electron micrographs of cortical pyramidal neurons revealed significantly increased mitochondrial cristae density in both Slack KO and Slack-R455H mice. Assessment of reactive oxygen species (ROS) disclosed a significant elevation in Slack-R455H neurons, whereas no significant change was detected in Slack KO. Taken together, these findings reveal that loss- and gain-of-function states converge on shared structural mitochondrial remodeling through mechanistically distinct pathways: gain-of-function mutations couple excessive potassium current in the plasma membrane to oxidative stress and bioenergetic insufficiency, whereas the Slack KO phenotype likely reflects non-conducting roles of the Slack C-terminal domain in cristae organization. We propose that Slack acts as a bidirectional regulator of mitochondrial homeostasis, and that disruption of this regulatory axis contributes to the metabolic pathophysiology underlying both the seizure burden and cognitive impairments associated with Slack channelopathies.

Disclosures: H. Wang: None. **Y. Zhang:** None. **J. Wu:** None. **E.A. Jonas:** None. **L.K. Kaczmarek:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.04/H2

Topic: B.03. Ion Channels

Support: NHLBI Grant R01HL102758

Title: Motor circuit alterations in gain-of-function KCNMA1 channelopathy

Authors: J. R. M. HARVEY[1], K. J. FLORES-FELIX[2], B. JUAREZ[3], ***A. L. MEREDITH**[4,1]; [1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Anat. and Neurobio., Univ. of Maryland Baltimore, Baltimore, MD; [3]Pharmacol., Univ. of Maryland, Baltimore, Baltimore, MD; [4]NINDS, North Bethesda, MD

Abstract: *KCNMA1* encodes the brain and muscle enriched large conductance voltage- and Ca^{2+}-activated K^+ channel (BK). Human gain-of-function (GOF) variants cause *KCNMA1* channelopathy, an ultra-rare neurological disorder presenting with motor dysfunction (atonic paroxysmal dyskinesia and/or ataxia), epilepsy, developmental delay, and intellectual disability. More than one-third of individuals in the patient cohort carry the N999S and D434G GOF *KCNMA1* variants, and transgenic mouse models harbouring these mutations display lower

seizure thresholds and mixed motor dysfunction. However, the brain loci and cellular mechanisms underlying these phenotypes remain poorly understood. To identify neuronal differences associated with motor circuit dysfunction, we analysed gene expression differences from the striatum and cerebellum of wildtype (WT) and transgenic ($D434G^{+/-}$, $D434G^{-/-}$, and $N999S^{+/-}$) mice and assessed excitability in D1-expressing medium spiny neurons (MSNs) recorded from acute striatal slices. Transcript analysis using mouse Clariom D microarrays revealed ~4-fold more differentially expressed genes (DEGs) in cerebellum compared to striatum across all three genotypes combined (181 versus 46 DEGs), with individual DEGs in cerebellum from $D434G^{+/-}$, 105; $D434G^{-/-}$, 91; $N999S^{+/-}$, 18 and in striatum from $D434G^{+/-}$, 30; $D434G^{-/-}$, 23; $N999S^{+/-}$, 6. Qualitatively, DEGs in $D434G^{+/-}$ and $D434G^{+/+}$ suggested widespread disruption of MSN and Purkinje cell function (eg: GPR88 in striatum and KCNC3 in cerebellum) that was greater for $D434G^{-/-}$ compared to $D434G^{+/-}$, consistent with a gene dosage effect. $N999S^{+/-}$ DEGs pointed towards mild neuromodulatory changes (eg: CCK in striatum, NOS1 in cerebellum) rather than disruptions of core function. Whole-cell current clamp recordings from $N999S^{+/-}$ striatal D1-MSNs showed a 27% increase in action potential firing at 150pA current injection, but the overall input-output relationship was not significantly different between genotypes ($p=0.36$, 2-way repeated measures ANOVA). Together these findings reveal that GOF *KCNMA1* variants engage distinct gene expression profiles in mouse disease models, providing a basis for understanding how the underlying neuronal dysfunction contributes to the spectrum of motor phenotypes in *KCNMA1* channelopathy.

Disclosures: J.R.M. Harvey: None. **K.J. Flores-Felix:** None. **B. Juarez:** None. **A.L. Meredith:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.05/H3

Topic: B.03. Ion Channels

Support: NIH Grant R15DK140842
App State Undergraduate Research Council
App State SAFE Award
App State Office of Student Research Grants

Title: Utilizing estrogenic regulation of orexin neurons to reveal cellular heterogenity

Authors: A. M. DURHAM, V. M. WEBSTER, *T. L. STINCIC;
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Abstract: Introduction: Despite relatively few in number, hypothalamic orexin (ORX) neurons influence diverse behaviors including arousal, locomotion, anxiety, and food consumption. Previous reports have identified heterogeneity in ORX neurons suggestive of at least two

functionally distinct subpopulations. The first regulates reward motivation and selectively expresses the A-type K+ current. The second subpopulation stimulates activity and is tonically depolarized by a non-selective cation current (TRPC5-mediated). Based on the well-characterized effects of estradiol (E2) over female rodent behavior, we hypothesized that ORX subpopulations display differential sex differences and estrogenic regulation based on their behavioral domains.
Methods: Male mice were kept intact while female mice underwent ovariectomy and, after 7-10 days, received either vehicle (oil) or E2 replacement. First, individually harvested ORXeGFP neurons (10-cell pools, 4 pools/group) underwent RT-PCR before qPCR to quantify differences in gene expression between groups. Pdyn expression was increased and Vglut2 expression decreased in E2 pools compared to vehicle ($p<0.05$). A trend was observed for Hcrt to decrease and Kcnd3 to increase ($p=0.09$) with E2. Trpc5 was not detected. Based on these results, in situ hybridization was used to determine co-localization patterns and E2 regulation of Trpc5 (cation current), Kcnd3 (A-type K+ channel subunit), and Pdyn (dynorphin) in *Hcrt*+ (prepro-orexin) neurons. We then conducted electrophysiology to confirm the physiological significance of these molecular findings. Finally, we mapped close contacts between hypothalamic arcuate and orexin neurons to examine differential connectivity between subpopulations.
Conclusions: While previous reports have found sex differences in ORX-related behaviors, we believe this is the first study conclusively demonstrating estrogenic regulation of ORX neuron gene expression. These findings suggest that E2 biases ORX neurotransmission to a net inhibitory output. We are in the process of analyzing in situ data, mapping, and electrophysiology data. If preliminary results are confirmed, these changes in excitability and neurotransmission could explain how E2 selectively regulates ORX neurons to increase activity while simultaneously diminishing food motivation.

Disclosures: A.M. Durham: None. **V.M. Webster:** None. **T.L. Stincic:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.06/H4

Topic: B.03. Ion Channels

Support: Intramural Research Program of the National Institutes of Health

Title: Preso1 regulates voltage-gated potassium channel Kv4.2, impacting hippocampal excitability, synaptic plasticity, and adaptive behavior

Authors: *M. A. WELCH[1], J.-H. HU[3], K. JEROME[4], Y. LIU[2], D. A. HOFFMAN[1]; [2]NICHD, [1]NIH, Bethesda, MD; [3]NICHD, Bethesda, MD; [4]Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD

Abstract: Preso1 (a.k.a. FRMPD4) is a post-synaptic scaffold protein shown to positively regulate excitatory synaptic transmission and spine density. Clinically, mutations in the *Preso1* gene cause X-linked intellectual disability and a *Preso1* variant is associated with an increased risk of cognitive decline in Alzheimer's disease. Previous work found Preso1 regulates metabotropic glutamate receptor (mGluR5) signaling by recruiting proline-directed kinases that phosphorylate S1126, generating a binding site for prolyl cis/trans isomerase Pin1. However, despite its significant clinical and synaptic relevance, Preso1 remains understudied. Interestingly, the Pin1 binding motif in mGluR5 (residues 1122-1130, L**TP**P**SP**FRD) is conserved in the voltage-gated potassium channel Kv4.2 (residues 601-610, P**TP**PVT**TP**EG), where the second TP/SP of the Pin1 docking site is regulated by proline directed kinases in an activity-dependent manner. We therefore hypothesized that Preso1 may also act as a scaffold protein for Kv4.2, regulating channel phosphorylation at T607 and modulating channel function. We found Kv4.2 channels directly bind to Preso1. Unexpectedly, rather than promoting phosphorylation by recruiting kinases to the complex, Preso1 instead recruits phosphatases PP1 and PP2A to de-phosphorylate Kv4.2 at T607 in response to neuronal activity. Functionally, the Kv4-mediated A-type potassium current (I_A) is reduced in hippocampal CA1 neurons in Preso1 knock out (KO) mice. Pharmacological inhibition of PP1/PP2A reduced I_A in wild-type (WT) neurons, while this effect was mimicked and occluded by loss of Preso1. Consistent with reduced I_A, Preso1 KO mice displayed enhanced somatic and dendritic hippocampal excitability. While basal synaptic transmission was unchanged, hippocampal synaptic plasticity, including long-term potentiation (LTP), long-term depression (LTD) and depotentiation were significantly impaired following loss of Preso1. These deficits translated to behavioral impairments in cognitive flexibility, including deficits in Morris water maze reversal learning and extinction during fear conditioning. Together, these findings reveal a novel role for Preso1 as a phosphatase scaffold for Kv4.2 and establish Preso1 as critical regulator of intrinsic excitability, synaptic plasticity, and adaptive behavior.

Disclosures: M.A. Welch: None. **J. Hu:** None. **K. Jerome:** None. **Y. Liu:** None. **D.A. Hoffman:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.07/H5

Topic: B.03. Ion Channels

Support: R21NS125503
U54NS108874
R01NS137587
New York Stem Cell Foundation

Title: Machine learning resolves functional phenotypes and therapeutic responses in KCNQ2 developmental epileptic encephalopathy iPSC models

Authors: *D. SIMKIN[1], S. M. WAFA[2], Y. YANG[1], M. GHARIB[1], K. A. MARSHALL[1], R. BANJO[1], C. REYES[1], A. L. GEORGE, JR[2], E. KISKINIS[1];
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Abstract: Pathogenic variants in *KCNQ2*, encoding the voltage-gated K^+ channel $K_v7.2$, cause developmental and epileptic encephalopathy (KCNQ2-DEE), characterized by neonatal seizures and lifelong neurodevelopmental deficits with no effective treatments. Using iPSC-derived cortical excitatory neurons from 6 patients carrying distinct heterozygous *KCNQ2* mutations (R207W, H228R, T274M, F305del, P335L, R581Q) and CRISPR/Cas9-corrected isogenic controls, we investigated shared and patient-specific pathophysiological mechanisms. Gene expression profiling revealed consistent upregulation of Ca^{2+}-activated small conductance K^+ (SK) channel genes *KCNN1* and *KCNN2* across all 6 patient lines at day 35 *in vitro*, accompanied by enhanced slow post-burst afterhyperpolarizations (sAHPs) measured by current-clamp recordings. Pharmacological blockade of K_v7 channels with XE991 in isogenic control neurons recapitulated both SK channel transcriptional upregulation and disease-associated functional phenotypes, while inhibition of other K^+ channels with 4AP did not, demonstrating the specificity of M-current loss in driving maladaptive SK channel compensation.
To dissect functional consequences across distinct patient mutations, we combined MEA recordings with supervised and unsupervised machine learning (ML) to characterize time-dependent neuronal phenotypes over 5 weeks *in vitro*. Supervised classifiers identified three robust DEE biomarkers, all enhanced in DEE patient lines: spike count Fano factor, ISI CV, and network burst duration, which collectively reflect irregular spike timing and stronger network bursting. T-PHATE dimensionality reduction further resolved distinct temporal functional trajectories in KCNQ2-DEE neurons relative to isogenic controls. Despite shared biomarker signatures, chronic retigabine treatment produced variable and largely incomplete rescue of SK channel expression and MEA phenotypes across patient lines, revealing patient-specific determinants of pharmacological response. To confirm specificity of the KCNQ2-DEE phenotypic signature, we extended our cohort to include a self-limited neonatal epilepsy line (E257GfsX6) and a gain of function DE line (R201H). These comparisons revealed clinical subtype-specific MEA phenotypes and SK channel profiles distinct from the DEE signature, demonstrating the ability of iPSC models to capture critical disease context. These results establish maladaptive SK channel upregulation as a convergent, DEE-specific pathophysiological mechanism and position our MEA-based ML framework for biomarker discovery and therapeutic evaluation in iPSC neuronal models.

Disclosures: D. Simkin: None. **S.M. Wafa:** None. **Y. Yang:** None. **M. Gharib:** None. **K.A. Marshall:** None. **R. Banjo:** None. **C. Reyes:** None. **A.L. George, Jr:** None. **E. Kiskinis:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.08/H6

Topic: B.03. Ion Channels

Support: NIH/NICHD Intramural Grant 1ZIAHD001205-33
NIH/NICHD Intramural Grant 1ZIAHD008755-20

Title: The Kv4 macromolecular complex as a target to manipulate neural activity within the habenulo-interpeduncular axis: potential implications in addiction-related phenotypes

Authors: *V. K. CHITTAJALLU[1], C. MALLOY[2], A. CACCAVANO[1], L. LIN[2], X. YUAN[1], A. VLACHOS[1], D. ABEBE[1], S. HUNT[1], J.-H. HU[2], E. LONDON[1], K. A. PELKEY[1], D. A. HOFFMAN[2], C. J. MCBAIN[1];
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Abstract: The medial habenula to interpeduncular (mHb-IPN) axis serves as a relay between limbic forebrain and downstream dopaminergic/serotonergic nuclei thus is anatomically well-placed for emotion and reward processing. Indeed, mHb-IPN activity is linked to various anxiety and addiction related behaviors, and perturbation of signaling within these structures can sculpt these conditions. Potassium channels comprise a molecularly diverse ion channel subfamily, that regulate neuronal excitability and circuit dynamics. Leveraging publicly available transcriptomic datasets (Allen Brain Knowledge Platform), we identify robust expression of *Kcnd2* and *Kcnd3* mRNA that encode the pore-forming subunits of Kv4 transient potassium channels (I_A), along with transcripts of their auxiliary partners (DPPX and KChIPs) in the mHb. In fact, *Kcnd2* and *Dpp6* are among the most highly expressed transcripts (>99th percentile) within the mHb cholinergic neuronal population. At the protein level, we demonstrate strong Kv4 expression in mHb cholinergic neurons with notable enrichment at the soma membrane pointing to a potential role in modulating their function. We have performed a comprehensive physiological analysis of Kv4 mediated I_A in mHb cholinergic neurons and demonstrate that this conductance critically regulates their tonic firing frequency. Interestingly, genetic ablation of the auxiliary protein, DPP6, causes a shift in Kv4 protein expression from its predominant soma location into the axonal tracts and terminals located in the fasciculus retroflexus and interpeduncular nucleus, respectively. This remarkable redistribution manifests as an augmented frequency in the tonic firing of mHb cholinergic neurons. If and how this mis-localization affects glutamatergic/cholinergic synaptic transmission onto postsynaptic GABAergic IPN neurons is currently under investigation. It is well known that repeated drug exposure (e.g. nicotine, alcohol, opioids, and cocaine) can result in protracted changes of the mHb-IPN circuitry. Given the strong expression of addiction-linked nicotinic receptor subunits (α3/α5/β4) in this pathway, our ongoing work is examining whether nicotine exposure impacts Kv4 function in mHb cholinergic neurons via activity-dependent plasticity mechanisms akin to that characterized in CA1 pyramidal cells. Finally, we will assess whether conditional DPP6 deletion from mHb cholinergic neurons sculpts behaviors associated with nicotine intake. Together, the current study will determine whether the Kv4 macromolecular complex constitutes a viable therapeutic target for modulating addiction-related behaviors.

Disclosures: V.K. Chittajallu: None. **C. Malloy:** None. **A. Caccavano:** None. **L. Lin:** None. **X. Yuan:** None. **A. Vlachos:** None. **D. Abebe:** None. **S. Hunt:** None. **J. Hu:** None. **E. London:** None. **K.A. Pelkey:** None. **D.A. Hoffman:** None. **C.J. McBain:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.09/H7

Topic: B.03. Ion Channels

Support: NIH grant 1ZIANS003135

Title: Effects of silent Kv9.3 subunit expression upon Kv2.1 clustering and calcium signaling in midbrain dopamine neurons

Authors: *R. DICK[1], Z. M. KHALIQ[2];
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Abstract: Electrically silent Kv9.3 potassium channel subunits form heteromers with Kv2.1 voltage-gated potassium channels and affect their kinetic and pharmacological properties. However, it is unknown whether Kv9.3 expression affects the non-conducting role of Kv2.1 clusters to link the endoplasmic reticulum (ER) and plasma membrane (PM), which facilitates calcium storage in the ER during neuronal activity. Since Kv9.3 expression is higher in midbrain dopamine neurons of the substantia nigra (SNc), which are more vulnerable to cell death in Parkinson's disease (PD) compared to dopamine neurons in ventral tegmental area, we hypothesize that Kv9.3 expression disrupts the formation of Kv2.1 clusters at ER-PM junctions and leads to altered intracellular calcium levels. We will use RNAscope and Western blots to quantify Kv2.1 expression and immunohistochemistry to measure the density of Kv2.1 clusters in midbrain dopamine neurons of Kv9.3 knockout mice and wild-type littermates. We will also use calcium imaging and whole-cell patch clamp electrophysiology in acute brain slices to determine whether calcium levels in the ER are affected in SNc neurons. We expect to see a decrease in ER calcium storage during neuronal activity driven by a loss of ER-PM junctions in Kv9.3 knockout mice, with a corresponding increase in cytosolic calcium leading to higher calcium-induced calcium release mediated by SK channels. This project will contribute to our understanding of the relationship between potassium channel expression, ER calcium storage, and dopaminergic cell death in PD.

Disclosures: R. Dick: None. **Z.M. Khaliq:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.10/H8

Topic: B.03. Ion Channels

Support: NIH Grant R01-AA011560

Title: Serine 160 of the BK channel $\beta_1$subunit mediates alcohol-evoked reduction of channel activity and eventual constriction of cerebral arteries.

Authors: *S. MYSIEWICZ[1], S. THAPA[1], S. HAWKS[2], S. JAYARAMAN[2], A. BUKIYA[2], A. DOPICO[2];
[1]PhAST, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]PhAST, The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Binge drinking is the most prevalent form of excessive alcohol consumption and accounts for numerous alcohol-related deaths. Ethanol (EtOH) at concentrations reached in blood upon binge drinking (≥35 mM) causes alcohol-induced blackouts (AIB), with hippocampal CA1-mediated memory being particularly disrupted. Of note, such EtOH concentrations constrict both large cerebral arteries and intraparenchymal arterioles irrigating CA1, an EtOH action that may contribute to CA1 dysfunction, as this brain region has a high metabolic rate and critically depends on oxygen for proper function. Delivery of oxygen and nutrients require proper smooth muscle (SM) tone and artery diameter, which are primarily determined by the activity of SM voltage-/Ca^{2+}-gated K^+ channels of big conductance (BK). In cerebral artery SM, BKs include regulatory β_1 subunits, which consist of two small intracellular tails, two transmembrane (TM) domains, and an extracellular loop. Interestingly, the β_1 TM2 is required for EtOH to inhibit SM BKs and evoke cerebral artery constriction (*Kuntamallappanavar & Dopico, 2017*). The goal of the present study is to identify the molecular site(s) in β_1TM2 that mediates EtOH inhibition of SM BKs and constriction of cerebral arteries. Computational modeling using AutoDock4.2 shows that Ser160 of β_1 TM2 is a key residue for EtOH docking. Next, to probe this residue in EtOH action, we performed: (1) inside-out (I/O) patch clamp on isolated SM myocytes from middle cerebral arteries; (2) diameter tracing of ex vivo pressurized middle cerebral arteries, and (3) simultaneous CA1 pyramidal neuronal firing and CA1 hippocampal arteriole diameter measurements *in vivo* from wild type (C57BL/6J) and *Kcnmb1S160A* littermate mice. Data show that EtOH inhibition of MCA SM BKs from *Kcnmb1S160A* mice is significantly reduced when compared to wild type. Consistently, the β_1S160A substitution ablates EtOH-induced artery constriction ex vivo. Miniscope data on the effects of EtOH on CA1 arteriole diameter and concurrent pyramidal neuron firing are being analyzed. Together, this study for the first time advances Ser160 of the BK regulatory β_1 subunit as a site for EtOH recognition to inhibit cerebral artery BKs and evoke eventual vasoconstriction. Our work opens the possibility of β_1S160-targeted pharmacological intervention to counteract hippocampal ischemia associated with AIB.

Disclosures: S. Mysiewicz: None. **S. Thapa:** None. **S. Hawks:** None. **S. Jayaraman:** None. **A. Bukiya:** None. **A. Dopico:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.11/I1

Topic: B.03. Ion Channels

Title: Biophysical properties and peptide modulation of K_V10.1 using high throughput automated patch clamp

Authors: N. BRINKWIRTH[1], M. ROTORDAM[1], A. K. SUNDMAN[2], N. SAEZ[2], **A. R. OBERGRUSSBERGER**[1], N. BECKER[1], E. DRAGICEVIC[1], *Y.-L. LU[3], G. KING[2], N. FERTIG[1];
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Abstract: K_V10.1, encoded by KCNH1, is a brain-enriched voltage-gated potassium channel implicated in developmental and epileptic encephalopathies. Pathogenic KCNH1 variants typically confer gain-of-function effects that increase neuronal excitability, and K_V10.1 is a potentially promising target for epilepsy. One of the challenges in targeting K_V10.1 is its similarity to the cardiac K_V11.1 (hERG) channel and any potential drugs must be highly selective for K_V10.1. In addition, the goal is to identify gating modulators that restore function, rather than pore blockers. In this study we recorded K_V10.1 using high throughput automated patch clamp (SyncroPatch 384) and compared this with K_V11.1. The current-voltage curve for K_V10.1 revealed a Vhalf of activation of ~22mV compared with ~13 mV for K_V 11.1 at room temperature (RT). Increasing temperature to 37°C shifted the Vhalf of activation of K_V10.1 by approximately 10 mV to more negative potentials. We were also able to assay 9 analogues (14 compounds including isoforms) of a lead peptide candidate against both K_V10.1 and K_V11.1 channels simultaneously, and determine (i) a site that changes the selectivity for K_V11.1 vs. K_V10.1 (compound 14) which we hope will enable reverse-engineering the selectivity, and (ii) determine which residues are essential for binding (inactive compounds), using only small amounts of peptide (<100 µg). In another set of experiments we screened a large number of venom fractions (111 in total) to identify which fractions were bioactive and simultaneously rule out candidates with off-target effects, a very important factor for this target. This process is normally laborious, taking many months, and off-target screening is typically done much later. Using high throughput automated patch clamp, this screening was possible in just a few days and provides a promising method for identifying peptides isolated from venom fractions that are selective for K_V10.1 over K_V11.1.

Disclosures: N. Brinkwirth: A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **M. Rotordam:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **A.K. Sundman:** None. **N. Saez:** None. **A.R. Obergrussberger:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **N. Becker:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **E. Dragicevic:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH. **Y. Lu:** A. Employment/Salary (full or part-time):; Nanion Technologies, Inc.. **G. King:** None. **N. Fertig:** A. Employment/Salary (full or part-time):; Nanion Technologies GmbH.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.12/I2

Topic: B.03. Ion Channels

Support: BBRF Young Investigator

Title: Expression pattern of Kv3 potassium channel subunits in dopaminergic neurons of the ventral tegmental area

Authors: *A. QUINTERO[1], C. TSCHUMI[2];
[1]Psychology, [2]Univ. of Texas at El Paso, El Paso, TX

Abstract: Mesostriatal pathway dysfunction is implicated in a range of psychiatric and developmental conditions, including substance use disorder, schizophrenia, and autism spectrum disorder. Within this pathway, network activity in the ventral striatum and its inputs from the ventral tegmental area (VTA), which release the neurotransmitter dopamine, regulate reward-related behaviors that are impaired in these disorders. Deficits in mesostriatal network activity and dopamine-dependent behaviors may be driven by alterations in the brain-wide function of specific ion channels. Here we focus on the Kv3 voltage-gated ion channel (Kv3), as genetic mutations in Kv3 channels have been identified in the disorders listed above. However, little is known about the pattern of expression of Kv3 channels in the VTA. Kv3 channels are composed of four subunits (Kv3.1 - Kv3.4), encoded by genes KCNC1 - KCNC4. Here we examined Kv3 subunit expression in the ventral tegmental area (VTA), which is the origin of mesostriatal dopaminergic projections. RNAscope was used to visualize *Kcnc1, Kcnc2, Kcnc3 and Kcnc4* gene expression in tyrosine hydroxylase (TH)-expressing cells of the mouse VTA. Expression patterns were quantified using semi-automated image analysis with open source softwares Qupath and Fish to Figure. *Kcnc* genes are usually co-expressed within single neurons. 57% of dopamine neurons expressed *Kcnc1*, while 70% expressed *Kcnc2*. Expression of *Kcnc1* by itself was observed in only 5% of dopamine neurons. 51% of neurons co-expressing *Kcnc1* and *Kcnc2* were TH-positive cells. *Kcnc3* was present in approximately 67% of dopamine neurons, but it was by itself in only 10% of those cells. We found that *Kcnc3* and *Kcnc4* are co-expressed in 57% of dopamine neurons. Interestingly, *Kcnc4* is predominantly expressed in non-dopamine cells. It was present in 68% of non-Th cells, although it is still present in a subset of dopamine neurons. *Kcnc1* and *Kcnc2* are frequently co-expressed in dopamine neurons, which suggests that these channels may form heteromeric complexes that shape neuronal firing properties. This may explain why dysregulation of KCNC1 is associated with substance use disorder and schizophrenia. Understanding how these subunits are distributed at a cell-type level may help explain how ion channel dysfunction contributes to abnormal dopamine signaling.

Disclosures: A. Quintero: None. **C. Tschumi:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.13/I3

Topic: B.03. Ion Channels

Support: R01-ES031407

Title: BK channel β_1 subunits reduce toluene-induced BK channel inhibition and consequent cerebral artery constriction.

Authors: *A. A. SHAW[1], S. C. MYSIEWICZ[1], A. N. BUKIYA[2], A. M. DOPICO[3]; [1]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [3]Pharmacol., The Univ. of Tennessee HSC, Col. of Medici, Memphis, TN

Abstract: Toluene (Tol) acute intoxication by inhalation and brain ischemia share many neurological and psychological outcomes. Previously, our group has shown that Tol at toxicologically relevant concentrations constricts rat and mouse middle cerebral arteries (MCA), an effect that is mediated by Tol-induced inhibition of voltage/Ca^{2+}-gated, large-conductance potassium (BK) channels in vascular smooth muscle (SM) (Shaw et al., 2025). These channels include channel-forming α and regulatory β_1 subunits (Dopico et al., 2018). Since the latter are involved in determining the final effect of cerebrovascular BK channel modulators, whether endogenous such as progesterone (North et al., 2023), or exogenous such as alcohol (Bukiya et al., 2009), we sought to investigate the role of β_1 subunits in Tol action on these channels. Thus, we evaluated the effect of acute Tol exposure on the function of BK channel homotetramers made of α subunits cloned from rat cerebral artery SM (cbv1 channels) in the presence and absence of β_1 subunits following channel reconstitution into 3:1 (w/w) phosphatidylethanolamine: phosphatidylserine planar bilayers. Tol (0.1 mM) caused a 40% reduction in channel open channel probability (Po). When β_1 was present, however, this inhibition was diminished to a 16.5% reduction of pre-Tol Po. Neither homomeric cbv1 nor heteromeric cbv1+β_1 channels modified unitary current amplitude in presence of Tol. To test whether Tol action on BK Po translated into modification of organ physiology, diameter of isolated MCA from C57BL/6 $\beta_1^{-/-}$ mice and their wildtype counterparts was evaluated upon pressurization at 60 mmHg to allow development of physiological SM tone. In male and female MCA whose endothelial layer was removed by passing an air bubble for 90 seconds through the lumen (Liu et al., 2004; Shaw et al., 2025), 0.1 mM Tol induced a greater MCA constriction in $\beta_1^{-/-}$ than in wildtype mice, consistent with the reduced action of Tol in β_1-containing SM BK channels. This difference in Tol effect on diameter was seen in endothelium-intact female, but not male, MCA which suggests potential involvement of a sex-dependent endothelial factor(s) in Tol action on diameter of arterial segments with intact endothelium. Preliminary data from cranial windows suggest that β_1 modulation occurs *in* vivo as well, with $\beta_1^{-/-}$ mice experiencing a greater MCA constriction by 0.1mM Tol than their wildtype counterparts. Our study demonstrates that β_1 protects against Tol-induced SM BK channel inhibition and the resulting MCA constriction.

Disclosures: A.A. Shaw: None. **S.C. Mysiewicz:** None. **A.N. Bukiya:** None. **A.M. Dopico:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.14/I4

Topic: B.03. Ion Channels

Support: R01-HL147315

Title: Tyr450 in the BK Channel α Subunit Mediates Pregnenolone-Induced Cerebral Artery Constriction

Authors: *S. THAPA[1], K. NORTH[3], S. MYSIEWICZ[2], A. BUKIYA[5], A. DOPICO[4]; [1]Pharmacology, Addiction Science, and Toxicology, [2]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [4]Pharmacol., [3]The Univ. of Tennessee HSC, Col. of Medici, Memphis, TN; [5]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Pregnenolone is a neurosteroid that influences neuronal activity, glial growth, and various brain functions such as cognition, memory and mood regulation. It has also been shown to cause cerebrovascular constriction through inhibition of big conductance, Ca^{2+}- and voltage-activated potassium (BK) channels. However, the molecular site and the mechanism underlying the action of pregnenolone on BK channels remain unknown. Molecular docking using the BK α subunit (i.e., slo1 protein) identified slo1Tyr450 as a potential pregnenolone-recognition site. Here, we investigated the mediation of Tyr450 on pregnenolone-induced smooth muscle BK channel inhibition and cerebral artery constriction in wild-type and slo1 Y450F knock-in C57BL/6J mice bred from the same parental background. We examined pregnenolone actions on channel activity in inside-out membrane patches from arterial smooth muscle cells, and on ex vivo artery diameter in pressurized, de-endothelialized middle cerebral arteries. Pregnenolone was tested at 10 μM, a concentration which produces the maximum arterial constriction in wild-type mice. In these mice, pregnenolone decreased middle cerebral artery diameter in both sexes when compared with vehicle control (DMSO). The constriction to pregnenolone was larger in males (~4% decrease in diameter) than in females (~1.5%). This constriction, as well as pregnenolone-induced inhibition on BK channel activity in wild-type mice, remained consistent with our previous publications (North et al., 2021; 2022). Remarkably, both pregnenolone actions were ablated in slo1Y450F knock-in mice. These findings demonstrate that Tyr450 in the BK channel α subunit is required for pregnenolone-induced cerebral artery constriction through direct inhibition of BK channel activity. Together, our data identify a direct pregnenolone-recognition site in slo1 proteins, and the mechanism involved in pregnenolone-induced cerebral artery constriction. Support: R01-HL147315 (A.D.)

Disclosures: S. Thapa: None. **K. North:** None. **S. Mysiewicz:** None. **A. Bukiya:** None. **A. Dopico:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.15/I5

Topic: B.03. Ion Channels

Support: NIH UM1MH130981

Title: Functional role of potassium channel dynamics in transcriptomically-defined neuronal types in mouse primary visual cortex.

Authors: *C. VERGARA[1], K. NASIROVA[1], R. MANN[1], K. HADLEY[1], K. BLAKE[1], M. KOCH[1], A. MCCUTCHEON[1], T. CASPER[5], J. ARIZA TORRES[2], N. DEE[5], K. SMITH[3], E. LEIN[4], H. ZENG[3], B. E. KALMBACH[6], T. JARSKY[7], B. R. LEE[1];
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Abstract: Potassium channels play a critical role in neuronal function by shaping action potential kinetics, regulating membrane excitability and ultimately contributing to circuit dynamics. Using an expanded patch-seq protocol to include voltage-clamp measurements of the 'nucleated patch', we isolate the amplitude and kinetics of potassium currents in mouse primary visual cortex and human cortical neurons. These multimodal measurements enabled us to link peri-somatic macroscopic voltage-gated potassium channel kinetics with intrinsic electrical properties and transcriptomic signatures. We found potassium A-type (I_A) and slowly inactivating delayed rectifier current (I_K) were strongly associated with key electrophysiological features and varied across transcriptomically-defined types. Specifically, I_K was prominent in parvalbumin neurons and correlated with action potential width and firing rate. To investigate the conservation of potassium channel dynamics across species, we compared these measurements in homologous mouse and human types. By directly relating potassium currents to intrinsic properties and gene expression in individual neurons, we provide a deeper understanding of neuronal function and its contribution to cortical circuits. Ultimately, integrating these independent data modalities yields a more comprehensive and refined view of neuronal diversity in the mouse and human cortex.

Disclosures: C. Vergara: None. **K. Nasirova:** None. **R. Mann:** None. **K. Hadley:** None. **K. Blake:** None. **M. Koch:** None. **A. McCutcheon:** None. **T. Casper:** None. **J. Ariza Torres:** None. **N. Dee:** None. **K. Smith:** None. **E. Lein:** None. **H. Zeng:** None. **B.E. Kalmbach:** None. **T. Jarsky:** None. **B.R. Lee:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.16/I6

Topic: B.03. Ion Channels

Support: 1R21NS127229-01A1

Title: Electrophysiological Profiling of Glioblastoma and Glioma Stem Cells Using Patch-clamp Physiology and Computational Modeling

Authors: *S. JETTI[1], M. SHOREY[2], B. R. ARENKIEL[3], P. J. HORNER[4], R. ROSTOMILY[5]; [2]Neurosurg., [1]Houston Methodist, Houston, TX; [3]Mol. & Human Genetis and Neurosci., Baylor Col. of Med., Houston, TX; [4]Houston Methodist Res. Inst., Houston, TX; [5]Dept Neurol Surgery, Univ. Washington Sch. Med., Seattle, WA

Abstract: Glioblastoma (GBM) is a highly heterogeneous brain tumor shaped by diverse molecular and biophysical factors that collectively influence cellular behavior, including membrane potential that contribute to proliferation and invasion. However, electrophysiological measurements reported across GBM and glioma stem cell (GSC) models remain dispersed throughout the literature, and quantitative frameworks for integrating these data are still under development. To examine the electrophysiological landscape of GBM and GSCs, we first carried out whole-cell electrophysiological measurements from GBM and GSC cell lines and then performed a meta-analysis of published patch-clamp datasets. We characterize resting membrane potential, excitability, ionic conductances and passive membrane properties from these cell types and compared them with published literature. These datasets were integrated to compare electrophysiological properties across cell models and experimental conditions. Experimental measurements were further used to develop conductance-based biophysical models incorporating leak, sodium, and potassium currents. Model parameters were constrained using experimentally measured membrane properties and electrophysiological responses. In parallel, we are training a deep neural network surrogate model on simulated datasets to enable rapid exploration of model parameter space and electrophysiological phenotypes. Preliminary analyses suggest substantial variability in electrophysiological properties across GBM and GSC populations, both within our datasets and among published studies. Computational modeling provides a framework for investigating how this variability may relate to differences in cellular electrical state. Ongoing work is focused on expanding experimental datasets, refining model parameters, and exploring relationships between electrophysiological features and tumor-associated phenotypes. This combined experimental and computational approach provides a platform for systematic characterization of GBM electrophysiology and may facilitate future studies investigating the role of bioelectric properties in glioma biology.

Disclosures: S. Jetti: None. **M. Shorey:** None. **B.R. Arenkiel:** None. **P.J. Horner:** None. **R. Rostomily:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.17/I7

Topic: B.03. Ion Channels

Support: 1NIH NIAA 1R01AA027808-01A1 (CV-M)
RCMI-CCRHD U54 MD007600 (EF-R)
PR-INBRE-P20GM10347 (CLC)
NSF DBI-1337284 (MWM)
NIGMS-NIH 5P30GM149367 (JLD)

Title: BK Channel Alternative Splicing Determines Ethanol-Induced Wnt/β-Catenin Signaling Activation

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Abstract: Large conductance Ca^{2+}-activated potassium (BK) channels play important roles in regulating neuronal excitability and are known to participate in the development of alcohol tolerance, a neuronal adaptation process. Previous research demonstrated that prolonged ethanol exposure triggers activation of canonical Wnt/β-catenin signaling, which results in increased expression of β-catenin and causes persistent decreases in surface expression of BK channels. Alternative splicing is critical in alcohol molecular tolerance desensitization. However, it is unknown whether the second component of alcohol molecular tolerance, BK surface redistribution, is isoform-dependent. Here, we sought to examine whether ethanol-induced activation of Wnt/β-catenin signaling is isoform-specific in the context of BK channel function, specifically, in ZERO and STREX channels, two commonly found isoforms. Stably transfected and monoclonal BK channel-expressing HEK293 cells were subjected to clinically relevant ethanol treatment, and activation of Wnt/β-catenin signaling and BK channel expression/localization were analyzed. Activation of the Wnt/β-catenin signaling pathway by ethanol has previously been shown to be a key factor in ZERO-expressing cells, which correlated with a significant decrease in expression/localization of surface ZERO BK channels, indicative of ethanol-induced BK molecular tolerance. Currently, we present evidence that STREX-expressing cells lack activation of Wnt/β-catenin signaling in response to ethanol and have no ethanol-induced changes in BK channel expression/localization. In this way, the isoform-specific remodeling can allow neurons to minimize the effects of ethanol on potassium currents due to the selective localization of the STREX isoform, resistant to ethanol action. Thus, this study has provided evidence that alternative splicing of BK channels contributes to channel plasticity induced by ethanol and serves as a potential mediator of alcohol molecular tolerance.

Disclosures: A. Guevarez Galan: None. **S. Encarnacion Burgos:** None. **C. Velazquez-Marrero:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.18/I8

Topic: B.03. Ion Channels

Support: 1NIH NIAA 1R01AA027808-01A1 (CV-M)
RCMI-CCRHD U54 MD007600 (EF-R)
PR-INBRE-P20GM10347 (CLC)
NIGMS-NIH 5P30GM149367 (JLD)

Title: MiR-9 Activates Wnt/β-Catenin Signaling to Promote Ethanol-Induced BK Channel Redistribution

Authors: *S. ENCARNACION BURGOS[1], A. GUEVAREZ GALAN[2], G. ENCARNACION BURGOS[3], C. VELAZQUEZ-MARRERO[4];
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Abstract: Alcohol molecular tolerance is driven by adaptive changes in gene expression and intracellular signaling that modulate neuronal excitability. One key target is the large-conductance calcium- and voltage-activated potassium (BK) channel, whose alcohol-sensitive ZERO isoform undergoes ethanol-induced surface expression redistribution. Two mechanisms implicated in BK channel regulation are ethanol-induced microRNA-9 (miR-9) upregulation and activation of the canonical Wnt/β-catenin signaling pathway. We investigate whether miR-9 acts upstream of Wnt/β-catenin activation to control BK ZERO trafficking. To determine if ethanol-induced miR-9 upregulation is required for Wnt/β-catenin activation, we used HEK293 cells stably expressing BK ZERO, and combined miR-9 gain- and loss-of-function approaches with pharmacological modulation of Wnt/β-catenin signaling. We assessed membrane-bound, cytoplasmic, and nuclear β-catenin localization, canonical Wnt pathway activity, and BK ZERO surface expression following ethanol exposure. This approach allowed us to determine if miR-9 is necessary and sufficient to mediate alcohol induced Wnt/β-catenin signaling modulation. Our results indicate that increased miR-9 expression enhances Wnt/β-catenin signaling, promoting β-catenin accumulation and driving BK ZERO surface redistribution. Furthermore, miR-9 inhibition during ethanol exposure attenuated β-catenin activation and prevented ethanol-induced loss of surface BK ZERO expression. Pharmacological Wnt/β-catenin modulation supported placing this pathway downstream of miR-9. Together, these findings support a model in which ethanol-induced miR-9 functions upstream of canonical Wnt/β-catenin signaling to promote BK ZERO internalization. By linking ethanol exposure to β-catenin-dependent BK channel redistribution, miR-9 may represent a critical post-transcriptional mechanism contributing to alcohol molecular tolerance.

Disclosures: S. Encarnacion Burgos: None. **A. Guevarez Galan:** None. **G. Encarnacion Burgos:** None. **C. Velazquez-Marrero:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.19/J1

Topic: B.03. Ion Channels

Support: NIH Grant R01 NS137587

Title: Antisense oligonucleotide therapy rescues neuronal network dysfunction in human and mouse models of KCNH1 developmental and epileptic encephalopathy

Authors: *W. CHI[1], E. E. CORBETT[2], C. H. THOMPSON[2], D. SIMKIN[1], H. ADIL[1], N. HAWKINS[2], N. CALLOW[1], L. BARSE[2], A. L. GEORGE, JR[2], J. A. KEARNEY[2], E. KISKINIS[1];
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Abstract: Gain-of-function (GOF) variants in *KCNH1*, which encodes the voltage-gated potassium channel Kv10.1, cause developmental and epileptic encephalopathies and syndromic neurodevelopmental disorders characterized by seizures, intellectual disability, and developmental delay. In contrast, *KCNH1* loss-of-function is well tolerated in humans and mice, suggesting that gene suppression may represent a viable therapeutic strategy. Here, we developed gapmer antisense oligonucleotides (ASOs) targeting *KCNH1* and evaluated their efficacy in human induced pluripotent stem cell (iPSC)-derived neuronal and mouse models of *KCNH1* disease. In control iPSC-derived cortical neurons, *KCNH1*-targeting ASOs reduced *KCNH1* transcript and protein expression without altering neuronal network activity measured by multi-electrode array (MEA) recordings. We next examined neurons carrying the pathogenic *KCNH1* variants I494V or G375R. Both neurons exhibited abnormal network activity despite unchanged action potential firing properties. A single ASO treatment administered at day 34 of differentiation normalized network activity in both mutant lines to control levels. Notably, ASO treatment did not restore the hyperpolarized resting membrane potential observed in mutant neurons, indicating that rescue of network dysfunction occurs independently of correction of intrinsic membrane properties. To assess therapeutic efficacy in vivo, we treated a GOF *Kcnh1* knock-in mouse model with a *Kcnh1*-targeting ASO. ASO administration reduced seizure burden and significantly improved survival. Together, these findings demonstrate that distinct *KCNH1* GOF variants converge on a reversible network-level dysfunction and provide proof of concept that ASO-mediated suppression of *KCNH1* is a promising therapeutic strategy for *KCNH1*-associated developmental and epileptic encephalopathies. More broadly, our results highlight the potential of gene suppression therapies for epilepsy genes in which GOF variants cause disease and LOF is clinically tolerated.

Disclosures: W. Chi: None. **E.E. Corbett:** None. **C.H. Thompson:** None. **D. Simkin:** None. **H. Adil:** None. **N. Hawkins:** None. **N. Callow:** None. **L. Barse:** None. **A.L. George, Jr:** None. **J.A. Kearney:** None. **E. Kiskinis:** None.

Poster

PSTR213: Voltage-Gated Potassium Channels

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR213.20/J2

Topic: B.03. Ion Channels

Support: NIH 7R01NS145389

Title: Structural Basis for Functional Modulation of $K_{Ca}2.2$ channels by Alternative Splicing

Authors: Y. NAM[1], S. QIU[2], H. WULFF[3], ***M. ZHANG**[1];
[1]Univ. of Arizona, Phoenix, AZ; [2]Basic Med. Sci., Univ. of Arizona COM-PHX, Phoenix, AZ; [3]Pharmacol., Univ. of California, Davis, Davis, CA

Abstract: Small-conductance Ca^{2+}-activated K^+ ($K_{Ca}2.2$) channels are gated by a Ca^{2+}-calmodulin dependent mechanism. In neurons, alternative gene splicing gives rise to $K_{Ca}2.2$ channels with differential biophysical and pharmacological properties. A splice variant ($K_{Ca}2.2b$) possessing an ARK insertion at $K_{Ca}2.2$'s intracellular HB helix in the C terminal domain, exhibits reduced apparent sensitivity to Ca^{2+} and a small molecule modulator compared to a splice variant without the insertion ($K_{Ca}2.2a$), but the underlying mechanism is unknown. Here, we report cryo-electron microscopy (cryo-EM) structures of $K_{Ca}2.2b$ in complex with calmodulin and Ca^{2+}, alone or bound to two small molecules (NS309 and CyPPA), at 3.42, 2.78 and 3.48 angstrom resolution, respectively. The ARK insertion compromises the van der Waals force interactions between CaM and $K_{Ca}2.2b$, compared to $K_{Ca}2.2a$ lacking the ARK insertion, underlying $K_{Ca}2.2b$'s reduced Ca^{2+}-sensitivity. NS309 binds to a hydrophobic pocket between $K_{Ca}2.2b$'s $S_{45}A$ helix and CaM N-lobe, strengthening both the van der Waals forces and electrostatic interactions between the $K_{Ca}2.2b$ and CaM, which explains its positive modulation of the channel activity. In contrast, CyPPA binds to a hydrophobic pocket between $K_{Ca}2.2b$'s $S_{45}B$ and HA helices, modestly strengthening the van der Waals forces but not electrostatic interactions between the channel and CaM, which explains its role as a "null" modulator of $K_{Ca}2.2b$.

Disclosures: Y. Nam: None. **S. Qiu:** None. **H. Wulff:** None. **M. Zhang:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.01/J3

Topic: B.04. Synaptic Transmission

Support: University of Kentucky College of Health Sciences
Department of Biology, University of Kentucky

Title: Physiological effects of acute, high-dose exposure to various elemental metals in animal modelsPhysiological effects of acute, high-dose exposure to various elemental metals in animal modelsPhysiological effects of acute, high-dose exposure to various elemental metals in animal models

Authors: *J. L. KUPCHELLA[1], E. ELLIOTT[2], W. STOVALL[2], M. DE CASTRO[2], K. NEGLIA[2], M. BOURGEOIS[2], J. KIM[2], Y. KIM[2], S. BIERBOWER[4], A. TAUL[2], E. RICHARD[2], R. L. COOPER[3], L. DOLLOFF[2], S. PETERS[2];
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Abstract: Elemental metals in various states are essential for living organisms, with involvement in protein structural integrity, tissue scaffolding, receptor and ion channel regulation, and ionic balance. Even so, exposure to such metals in too great a quantity can be quite harmful, in plants and animals alike. These potentially deleterious effects should be studied, particularly given that exposure can occur through industrial activity, mining, or even unregulated dietary supplements. Currently, the only standard treatment for overdosing on most of these metals (Zn, Cr, Co, Mo, Se, Mn, Cu) is cessation of the exposure. Only Fe3+ has a more extensive procedure, via chelation in the blood to reduce circulating concentrations. Understanding the physiological effects of these metals better will also allow for better understanding of how to mitigate the harmful effects of overexposure; therefore, this investigation involved exposure of various models (cellular, tissue, or whole-animal preparations of invertebrates like crabs, crayfish, and fruit flies) to high, acute doses of the various metals to learn more about these effects. Muscle membrane potential, cardiac function, sensory neuron activity, synaptic transmission, nerve conduction, and survival were observed with variable ranges between 2.5 mg and 40 mg, depending on the metal and organism. A wide array of results are reported herein: for example, Se (10 mM) had minor effects on isolated tissue but resulted in death (on the scale of hours or days) in whole-animal preparations of crayfish or larval Drosophila, while Zn2+ and Co2+ (each 5 mM) had greater effects on tissues (in terms of extent and rapidity) but delayed effects with whole animal exposure. Similarly, Mg2+ (with concentrations ranging from 5mM to 20mM), blocks the voltage-gated Ca2+ channels and Na+ leak channels, which causes hyperpolarization of cells, reducing synaptic transmission. These findings represent just a few of the examples of how elevated metal concentrations may disrupt physiological processes.

Disclosures: J.L. Kupchella: None. **E. Elliott:** None. **W. Stovall:** None. **M. de Castro:** None. **K. Neglia:** None. **M. Bourgeois:** None. **J. Kim:** None. **Y. Kim:** None. **S. Bierbower:** None. **A. Taul:** None. **E. Richard:** None. **R.L. Cooper:** None. **L. Dolloff:** None. **S. Peters:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.02/J4

Topic: B.04. Synaptic Transmission

Support: DoW/USU Brain Tissue Repository and Neuropathology Research Program USU #PAT-74-10982
NIH Grant U01 AI 150578

Title: Long-term effects of gamma-radiation on synapses in the non-human primate striatum

Authors: *K. GROEN[1,2,4], K. HATCH[1,2,4], E. K. MURPHY[1,2,4], T. BENZINE[1,2,4], J. D. OLSON[5], J. M. CLINE[5], D. P. PERL[2,4], D. IACONO[1,2,3,4];
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Abstract: While the brain has typically been considered "radio-resistant," the long-term effects of radiation on normal brain tissue are not yet well understood. Effects of gamma-radiation (γ-radiation) on the brain are hypothesized to vary based on the radiation duration, total dose absorbed, and body target, along with the specific brain region physiology and timing of analysis. Understanding the impact of radiation on the brain is crucial for civilian and military populations in efforts to mitigate the risks of and improve treatment strategies for environmental and occupational radiation exposure. To this end, we examined two relatively high doses of total-body γ-radiation in non-human primate (NHP) brains (rhesus macaques). NHP species provide the closest morpho-functional comparison to the human central nervous system. Adult male NHPs were exposed to a single dose of ~4 Gy (n=5) or ~8 Gy (n=4) γ-radiation and survived for approximately five years post-radiation, then were compared to age-matched controls (n=5). We focused on the striatum, a complex region associated with multiple motor and non-motor functions. Due to the level of functional complexity and neuroplasticity of the striatum during normal development as well as various neurodegenerative diseases, we aimed to assess synaptic changes in this unique cohort of animals. To probe possible protein expression changes, Western blotting was performed on synaptosomal extracts from the striatum for a set of pre- and post-synaptic markers: synaptophysin (pre), PSD95 (post), and GAP43 (neosynaptogenic). Densitometric analysis showed an upward trend in GAP43 expression in both 4 Gy and 8 Gy-irradiated animals versus controls, suggesting the potential for persistent neuroplasticity phenomena following radiation. Preliminary proteomics also revealed a significant increase in several synaptic targets in animals irradiated at 4 Gy compared to controls, including Synapsin II (SYN2) and Syntaxin-Binding Protein I (STXBP1), both presynaptic vesicle-associated proteins. Fewer significant changes in synaptic proteins were seen in the 8 Gy cohort, illustrating a lack of a linear dose effect. Validation and contextualization of such targets is a pertinent future direction to understand radiation's long-term effects on synapses and the brain at large.
Disclaimer: The opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the Department of War, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

Disclosures: K. Groen: None. **K. Hatch:** None. **E.K. Murphy:** None. **T. Benzine:** None. **J.D. Olson:** None. **J.M. Cline:** None. **D.P. Perl:** None. **D. Iacono:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.03/J5

Topic: B.04. Synaptic Transmission

Support: NIH Grant R35NS116852-07

Title: Synapse-Specific Alterations in $GABA_A$ Signaling During Epileptogenesis

Authors: *T. SHIU[1], K. P. LILLIS[3], K. J. STALEY[2];
[2]Neurol., [1]Massachusetts Gen. Hosp., Boston, MA; [3]Neurol., Harvard Med. School, MGH, Charlestown, MA

Abstract: Epileptogenesis is associated with pathological alterations in GABAergic signaling, including depolarizing shifts in $GABA_A$ receptor-mediated responses. It remains unclear whether these changes reflect intrinsic effects of epileptogenesis or arise secondarily from recurrent spontaneous seizures. We addressed this using organotypic hippocampal slice cultures (OHSC), a model of trauma-induced epileptogenesis in which ictal-like events emerge around day in vitro 3 (DIV3) and increase through DIV21.
To measure synapse-specific $GABA_A$ signaling, presynaptic interneurons expressing stCoChR (an excitatory opsin that enables single-neuron stimulation) were individually stimulated with blue light, while postsynaptic pyramidal neurons were recorded using gramicidin perforated-patch recording, allowing E_{GABA} measurement without perturbing intracellular chloride. Recordings were obtained from dentate gyrus and CA1 neurons at early (DIV7-10) and late (DIV17-20) stages.In the dentate gyrus, but not CA1, later stages exhibited a significant depolarizing shift in E_{GABA}, accompanied by increased cell-to-cell and synapse-to-synapse heterogeneity. The range of E_{GABA} variability increased from ~5 mV at early stages to ~18 mV at later stages. Additionally, mean E_{GABA} in the dentate gyrus shifted from approximately −82 mV at early stages to −70 mV at later stages. These findings indicate disruption of chloride homeostasis and inhibitory signaling during epileptogenesis, which may enhance network excitability and seizure susceptibility. Furthermore, there was no significant correlation between synaptic strength or response latency between the two stages.
Ongoing studies will determine whether these synapse-specific alterations in E_{GABA} are associated with changes in intracellular and extracellular chloride concentrations. We will compare chloride levels in dentate gyrus and CA1 neurons at DIV7-10 and DIV17-20 to test whether depolarized and heterogeneous GABAergic signaling is driven by altered chloride homeostasis. Together, these experiments will clarify whether disrupted chloride regulation is a persistent feature of epileptogenesis and may help explain how inhibitory signaling becomes destabilized during the development of epileptic networks.

Disclosures: T. Shiu: None. **K.P. Lillis:** None. **K.J. Staley:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.04/J6

Topic: B.04. Synaptic Transmission

Title: Regulation of tumor proliferation by unlocking silent synapses on metastatic cancer cells

Authors: *A. HOUCEK[1], I. A. UZAY[2], L. M. MONTEGGIA[5], A. LINKOUS[3], E. T. KAVALALI[4];
[1]Vanderbilt Univ., Nashville, TN; [2]Pharmacol., Vanderbilt Univ., Nashville, Turkey; [3]Pharmacol., Vanderbilt Univ., Greenbrier, TN; [4]Vanderbilt Brain Inst., Vanderbilt Univ., Nashville, TN; [5]Vanderbilt Brain Inst., Nashville, TN

Abstract: Several studies have revealed deleterious synapse formation onto cancer cells within the brain tumor microenvironment, yet these synapses are ~100-fold weaker in presynaptic release rates and postsynaptic strength relative to *bona fide* synapses formed between neurons. Here, we find that most of the functional synapses on tumor cells are kept dormant and can be unlocked by overcoming $GABA_B$ receptor-mediated metabotropic signaling in neurons. Scavenging $G_{\beta\gamma}$ signaling in neurons increased presynaptic release probability on tumor cells and augmented cancer cell proliferation. Optical analysis of the tumor microenvironment revealed regulated secretion of neurotransmitters from tumor cells in response to $GABA_B$ receptor inhibition or electrical stimulation. These results reveal how cancer cells with a high propensity for brain metastasis leverage precise moments of aberrant excitation between neurons to engage reciprocal interactions that ultimately fuel cancer proliferation.

Disclosures: A. Houcek: None. **I.A. Uzay:** None. **L.M. Monteggia:** None. **A. Linkous:** None. **E.T. Kavalali:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.05/J7

Topic: B.04. Synaptic Transmission

Support: MH002386

Title: Secretion-synthesis coupling by PACAP in NS-1 pheochromocytoma cells: A model for metabotropic regulation of neurotransmitter biosynthesis and release in CNS

Authors: W. XU[1], T. MUSTAFA[2], A. KEITH[3], P. SULLIVAN[4], D. S. GOLDSTEIN[5], *L. E. EIDEN[6];
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Abstract: The neuropeptide PACAP is a family B Gs-coupled GPCR ligand for the PAC1 receptor that plays an important role in stress signaling in the peripheral and central nervous systems. PACAP acts as a neurotransmitter at the splanchnicoadrenomedullary synapse, and is required for epinephrine secretion and biosynthesis, and activation of gluconeogenesis and survival, during prolonged metabolic stress (Hamelink et al., Proc. Natl. Acad Sci USA 99: 461, 2002; Stroth et al., Endocrinol. 154: 330, 2013). In the brain, PACAP acts within multiple circuits to maintain stress-initiated behaviors (e.g. see Jiang et al., Biol. Psychiatr. 3: 673, 2023). We used NS-1 pheochromocytoma cells as a model to probe the mechanism(s) of signaling by PACAP and other family B Gs-coupled GPCR ligands leading to enhanced neurotransmitter secretion and biosynthesis in neuroendocrine cells. PACAP treatment (100 nM, one hour) elevated dopamine levels via increased L-dopa production, and selectively enhanced vesicle-stored dopamine secretion. Both processes were mimicked by the adenylate cyclase activator forskolin. Enhanced synthesis, but not secretion, was blocked by the protein kinase A inhibitor H89. Biosynthesis and secretion were similarly regulated by the family B ligands secretin, GLP-1 and VIP, upon expression of their cognate receptors in NS-1 cells. Thus, PACAP appears to regulate neurotransmitter biosynthesis via a cAMP to PKA pathway, whereas neurosecretion requires cAMP but not PKA. Based upon the expression or lack of expression of various genes encoding calcium channels and cyclic AMP sensors in NS-1 cells there are multiple final effectors for Gs-coupled neurosecretion, including TrpC channels as reported by Broker-Lai et al. EMBO J. 43, 5813, 2024). The cAMP sensor linking cAMP elevation to neurosecretion remains undetermined in NS-1 cells, although candidates in chromaffin cells include Epac, via activation of PLC-epsilon (see Chen et al., Mol. Biol. Cell 35, ar92, 2024). Brain levels of dopamine and its metabolite 3,4-dihydroxyphenyl acetic acid (DOPAC) were significantly depleted in PACAP knockout mice in the midbrain, which contains the dopaminergic cell bodies that project to striatum and elsewhere, suggesting that PACAP functions to modulate the synthesis of DA in CNS. Other family B Gs-coupled GPCRs may be important for maintaining neurotransmitter biosynthesis or release, depending on the location of their receptors, in the brain.

Disclosures: W. Xu: None. **T. Mustafa:** None. **A. Keith:** None. **P. Sullivan:** None. **D.S. Goldstein:** None. **L.E. Eiden:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.06/J8

Topic: B.04. Synaptic Transmission

Title: Characterization of CNS Drug Candidates Through Excitation-Inhibition Balance Measurements Using Manual Patch-Clamp Electrophysiology

Authors: *S. GRIGORYEV, M. HE, C. PETROSKI, D. LIU, **R. E. PETROSKI**; Neuroservices-Alliance, San Diego, CA

Abstract: Excitatory and inhibitory synaptic balance is a fundamental determinant of neuronal network function and a critical pharmacological endpoint in CNS drug discovery. Alterations in excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs) have been implicated in epilepsy, neurodevelopmental disorders, schizophrenia, and neurodegenerative diseases. Despite increasing interest in E/I modulation as a therapeutic strategy, robust electrophysiological platforms for direct assessment of synaptic balance remain limited. In this study, we used whole-cell patch-clamp recordings to assess E-I balance by measuring spontaneous EPSCs at -70 mV and spontaneous IPSCs at 0 mV in the same neurons. We evaluated the effects of several reference compounds targeting neuronal receptors for effects on E-I balance including NBQX (AMPA receptor antagonist), CX-614 (AMPA receptor positive allosteric modulator), gabazine ($GABA_A$ receptor antagonist), diazepam ($GABA_A$ receptor PAM), xanomeline (M1/M4 muscarinic agonist), and buspirone (5-HT1A receptor partial agonist). Excitatory and inhibitory synaptic components were quantified independently, allowing direct measurement of pharmacological shifts in E/I balance. These studies demonstrate the benefit of manual patch-clamp electrophysiology as a service platform for functional profiling of CNS drug candidates. The assay can support academic and industry programs requiring mechanistic evaluation of compounds affecting synaptic transmission, neuronal excitability, and circuit function.

Disclosures: S. Grigoryev: None. **M. He:** None. **C. Petroski:** None. **D. Liu:** None. **R.E. Petroski:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.07/K1

Topic: B.04. Synaptic Transmission

Support: R01NS134128
R01MH070727
R01MH081060

Title: Mechanisms Underlying Allopregnanolone Modulation of Inhibitory and Excitatory Neurotransmission

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Abstract: Neuroactive steroids (NAS) are natural derivatives of progesterone that are effective as exogenous treatments for postpartum depression. Allopregnanolone (AlloP), a NAS and an endogenous positive allosteric modulator (PAM) of the $GABA_A$ receptor, has been reported to have antidepressant effects. Allop modulates both the synaptic (γ2-containing) and extra-synaptic (δ-containing) $GABA_A$ receptors to mediate both phasic and tonic inhibition. AlloP's rapid and sustained effects on synaptic transmission have attracted considerable interest. However, the precise synaptic mechanisms regarding both spontaneous and evoked neurotransmission at excitatory and inhibitory synapses are not fully understood, hence this study. Synaptic currents were recorded through patch clamp electrophysiology following four treatment paradigms: acute perfusion, 1-hour, 24-hour, and 48-hour incubations with 100nM of allopregnanolone before recording miniature inhibitory post-synaptic current (mIPSC), miniature excitatory post-synaptic current (mEPSC), and evoked inhibitory post-synaptic current (eIPSC). Acute allopregnanolone treatment decreased mIPSC frequency while increasing the rise and decay times of individual events, with no change in amplitude. Longer incubations consistently reduced mIPSC frequency and significantly increased their amplitudes, rise, and decay times compared to controls. Evoked IPSCs showed no amplitude changes but demonstrated prolonged decay times at all time points. For excitatory transmission, mEPSCs displayed stable frequency and kinetics, but a significant amplitude increase was observed at 24 hours with allopregnanolone. The enhancement of mIPSC amplitude and decay reflects upregulated postsynaptic $GABA_A$ receptor function, causing increased chloride influx and extended inhibition. Prolonged decay in evoked IPSCs supports stabilized receptor channel openings via allopregnanolone binding. The lack of mEPSC frequency change suggests no effect on presynaptic glutamate release, while the delayed amplitude rise likely results from postsynaptic synaptic scaling, possibly involving the upregulation of AMPA receptors. The absence of decay changes for mEPSCs alongside amplitude shifts is consistent with a postsynaptic mechanism. Collectively, these findings show that allopregnanolone selectively modulates inhibitory synapses through rapid and sustained effects, influencing both spontaneous and evoked GABAergic transmission. Excitatory activity, on the other hand, shows a delayed and transient increase in amplitude, possibly indicating a form of synaptic plasticity.

Disclosures: S.Y. Olatunji: None. **L.M. Monteggia:** None. **E.T. Kavalali:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.08/K2

Topic: B.04. Synaptic Transmission

Support: R01AA028566
R01AA028566-S1 (Diversity Supplement)
P50AA017823
F31AA032198

Title: Prenatal alcohol exposure and acute alcohol: the role of CRFR1 in the extended amygdala

Authors: *S. WINCHESTER[1], M. R. DIAZ[2];
[1]Psychology: Behavioral Neurosci., State Univ. of New York, Binghamton, Binghamton, NY;
[2]Psychology, Binghamton Univ., Binghamton, NY

Abstract: Alcohol consumption among pregnant women continues to rise, increasing the risk of offspring developing Fetal Alcohol Spectrum Disorder (FASD). FASDs are a collection of diagnosable medical conditions that can include an increased risk for alcohol misuse, with the potential for developing alcohol use disorder. The extended amygdala, comprised of the central amygdala (CeA) and the bed nucleus of the stria terminalis (BNST), plays a key role in the addiction cycle and is enriched with corticotropin releasing factor (CRF) and its receptor type I (CRFR1), the dysregulation of which is implicated in alcohol misuse. Our lab has found that a single moderate prenatal alcohol exposure (PAE) can disrupt the function and expression of CRFR1 in the medial nucleus of the CeA (CeM) of adolescent rats. Furthermore, we've shown that PAE can alter the effects of acute alcohol (EtOH) on GABAergic transmission in an age-, sex-, and concentration-specific manner in the CeM, with effects in adults being cell-type specific. However, it remains unclear how these modifications impact downstream targets like the BNST. The aims of the current study were to assess the effect of PAE on 1) general BNST physiology, 2) EtOH modulation of GABA transmission in the BNST, and 3) EtOH modulation of GABA transmission from CeM CRFR1+ neuron inputs into the BNST of adult rats. To investigate this, male CRF1-Cre-tdTomato rats were bred with female wildtype Wistars, and pregnant dams were exposed to EtOH on gestational day 12, via intraperitoneal (i.p) injection. This consisted of a 1g/kg EtOH i.p (20 % EtOH in sterile saline), or sterile saline, then 2 hours later, a 2nd i.p. injection of .75g/kg EtOH was given, with a target BEC of 60-120 mg/dL. CRF_1-Cre-negative offspring were assigned to experiment 1 and 2 (~P80). Offspring expressing the transgene underwent stereotaxic surgery [postnatal day (P)70] receiving bilateral injections of a Cre-dependent channelrhodopsin virus and subsequently used for experiment 3 (~P140+). For all experiments, electrophysiology was performed in the anterior medial BNST to assess the actions of acute EtOH on GABAergic transmission. Preliminary data in wildtype animals suggests that PAE increased neuronal excitability in males at baseline. Furthermore, EtOH decreased GABA release in control males at a single concentration, while PAE males exhibited decreases at both tested concentrations, suggesting enhanced sensitivity to alcohol. Ongoing studies are using optogenetics to investigate how PAE may alter the synaptic activity from CeM CRFR1+ projection neurons that terminate in the BNST (experiment 3).

Disclosures: S. Winchester: None. **M.R. Diaz:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.09/K3

Topic: B.04. Synaptic Transmission

Title: Machine learning and High-Density Micro-Electrode Array recordings reveal regional differences in baclofen sensitivity across cerebellar Purkinje cell populations

Authors: *J. ARTINIAN, S. GRAF, B. BUISSON, O. TOURY, B. BUISSON;
Slice laboratory, Neuroservices Alliance, Le Puy Sainte Reparade, France

Abstract: Purkinje cells (PCs) exhibit spontaneous pacemaker activity that is essential for cerebellar information processing. High-density microelectrode arrays (HD-MEAs) provide an unprecedented opportunity to record extracellular activity from large populations of PCs with high spatial resolution. However, the complexity and volume of HD-MEA datasets require robust analytical approaches for reliable spike detection and characterization.
In this study, we established an *ex vivo* cerebellar slice preparation optimized for HD-MEA recordings and developed a custom machine-learning-based pipeline for automated detection and sorting of PC spikes. We first characterized the quality and stability of spontaneous PC recordings obtained with the HD-MEA platform. We then compared spike detection performance between conventional analysis methods and our home-made machine learning algorithm. The machine learning approach improved spike identification in complex recording environments while maintaining high detection accuracy across large-scale datasets.
To demonstrate the utility of this platform for pharmacological investigations, we examined the effects of baclofen, a GABA-B receptor agonist known to decrease PC activity. Bath application of baclofen induced a robust and dose-dependent reduction in spontaneous firing frequency across recorded PCs. Leveraging the extensive spatial coverage of the HD-MEA, we mapped pharmacological responses throughout the cerebellar cortex and quantified regional differences in baclofen sensitivity at the lobular level.
Our analyses revealed a heterogeneous response to baclofen across cerebellar regions. PCs located in anterior cerebellar lobules exhibited significantly lower sensitivity to baclofen-induced firing suppression compared with cells recorded in posterior lobules. These findings highlight previously underappreciated functional differences along the anterior-posterior axis of the cerebellum and demonstrate the value of combining HD-MEA technology with machine-learning-based analysis for large-scale electrophysiological and pharmacological studies.

Disclosures: J. Artinian: A. Employment/Salary (full or part-time):; Neuroservices Alliance. **S. Graf:** A. Employment/Salary (full or part-time):; Neuroservices Alliance. **B. Buisson:** A. Employment/Salary (full or part-time):; Neuroservices Alliance. **O. Toury:** A. Employment/Salary (full or part-time):; Neuroservices Alliance. **B. Buisson:** A. Employment/Salary (full or part-time):; Neuroservices Alliance.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.10/K4

Topic: B.04. Synaptic Transmission

Title: Cannabinoid receptor type 1 mediated disinhibition of claustrum projection neurons

Authors: *N. M. MAYBERRY, A. B. WULFF, B. N. MATHUR;
Pharmacol. and Physiol., Univ. of Maryland, Baltimore, Sch. of Med., Baltimore, MD

Abstract: Cannabis is the most commonly used illicit substance globally, with about 60 million United States citizens aged 12 and older reporting using cannabis in 2024. Notably, about 30% of cannabis users will develop cannabis use disorder. Both acute and chronic cannabis use disrupts cognitive network organization and is associated with impaired attention, impulse control and decision making that may foster further misuse. How this occurs is poorly understood. The claustrum supports cognitive network organization through extensive cortico-claustro-cortical pathways. Claustrum projection neurons are under strong inhibitory control by parvalbumin (PV)-expressing interneurons, which in other brain regions express cannabinoid type 1 receptors (CB1Rs). Therefore, we hypothesized that activation of CB1Rs on PV-expressing inhibitory interneurons in the claustrum results in decreased GABA release probability, leading to aberrant disinhibition of claustrum projection neurons. PV-Cre mice were bilaterally injected with a Cre-dependent channelrhodopsin (ChR2)-expressing anterograde traveling adeno-associated virus (AAV) into the claustrum and a retrogradely traveling AAV (rgAAV) expressing a fluorophore into the parietal association cortex to fluoresce claustrum neurons projecting to this cortical network node region. Using whole-cell patch clamp electrophysiology, we recorded from fluorescently labeled claustrum projection neurons and found that bath application of the CB1R agonist WIN55,212-2 (WIN) decreased optically-evoked inhibitory postsynaptic current (oIPSC) event amplitudes. We also observed an increase in oIPSC paired-pulse ratio, suggesting a decreased release probability of GABA. Supporting this, we found an increased inter-event-interval of spontaneous IPSC events. Taken together these data suggest that activation of CB1Rs on PV inhibitory interneurons may disinhibit claustrum projection neurons to ultimately give rise to cognitive network disruption and associated cognitive impairments.

Disclosures: N.M. Mayberry: None. **A.B. Wulff:** None. **B.N. Mathur:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.11/K5

Topic: B.04. Synaptic Transmission

Support: NIH 1ZIAHD008884-17

Title: GABAergic neurons in rhombomere 3 selectively regulate short interstimulus interval prepulse inhibition

Authors: H. SHARMA[1], G. KIRBY[1], N. MCGRORY[1], S. SEMENOVA[1], A. A. BHANDIWAD[1], J. SINCLAIR[1], *H. A. BURGESS[2,1];
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Abstract: Prepulse inhibition (PPI) is a conserved sensorimotor gating mechanism that depends on precise temporal processing of sensory inputs, yet the neural circuits underlying interstimulus interval (ISI) dependent PPI remain poorly understood. Here, we identify a hindbrain circuit that selectively regulates short-ISI PPI using the Gal4 driver lines y242 and y467 in zebrafish. Both lines showed overlapping expression in rhombomere 3 (R3), highlighting this region as a critical locus for short-ISI PPI modulation. Optogenetic activation of R3 neurons using blue light selectively enhanced PPI at short ISIs, demonstrating a causal role for these neurons in temporal gating. Molecular characterization revealed a medially localized gad1b-positive GABAergic population within R3. Targeted ablation of these R3 GABAergic neurons specifically disrupted short-ISI PPI. Anatomical analyses further showed direct projections of R3 GABAergic neurons to the Mauthner cells, a key component of the startle circuit, and selective ablation of y467 neuron synapses adjacent to the Mauthner cell lateral dendrite diminished only short-ISI PPI. Single cell sequencing of Mauthner neurons showed robust expression of the GABA receptor subunit gabra5. Consistent with this, gabra5 mutant larvae showed impaired PPI. Together, these findings establish an R3-mediated Mauthner inhibitory circuit that selectively controls short-ISI sensorimotor gating.

Disclosures: H. Sharma: None. **G. Kirby:** None. **N. McGrory:** None. **S. Semenova:** None. **A.A. Bhandiwad:** None. **J. Sinclair:** None. **H.A. Burgess:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.12/K6

Topic: B.04. Synaptic Transmission

Support: The Pew Latin American Fellows Program (to L.G.V.)

Title: GABA and glutamate co-releasing interneurons in auditory cortex

Authors: L. G. VATTINO[1], ***S. PAK**[3,2], C. MACGREGOR[4], B.-S. WU[5], H. SOHN[6], D. B. ARNOLD[7], A. E. TAKESIAN[8];
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Boston, MA; [5]Harvard Med. Sch., BOSTON, MA; [6]USC, Los Angeles, CA, ; [7]USC, Los Angeles, CA; [8]Otolaryngology, Massachusetts Eye and Ear, Boston, MA

Abstract: Neurons are traditionally classified as either excitatory or inhibitory, yet evidence suggests that some neuronal populations across diverse brain regions may be capable of releasing both GABA and glutamate. However, the function of GABA- and glutamate-co-releasing neurons in the cortex remains understudied. Here, we identified and characterized a population of layer 1 (L1) interneurons in mouse primary auditory cortex that co-expresses the molecular machinery associated with dual GABA and glutamate release. Using fluorescent in situ hybridization (FISH), we found that a subset of L1 neurons expresses transcripts encoding the vesicular glutamate transporter 3 (VGluT3), vesicular GABA transporter (VGAT), and GAD1/2, with nearly all of these $VGluT3^+/VGAT^+$ cells also expressing the interneuron marker gamma-synuclein (SNCG). Immunohistochemistry confirmed the co-expression of GABA and VGluT3 proteins in this population. We then combined intersectional viral strategies with Brainbow-based single-cell labeling to show that these $VGluT3^+/VGAT^+$ interneurons are distributed across layer 1 and extend axons into deeper cortical layers. To identify their postsynaptic targets, we leveraged a novel anterograde transsynaptic tracer, ATLAS, which uses antibody-like proteins directed against postsynaptic receptors (e.g., AMPA or GABAA receptors) to drive Flp-dependent reporter expression selectively in neurons receiving either glutamatergic or GABAergic synapses from a genetically defined presynaptic population. ATLAS tracing from $VGluT3^+/VGAT^+$ neurons, combined with ChR2-assisted optogenetic activation and whole-cell recordings, revealed postsynaptic neurons that receive both inhibitory and excitatory postsynaptic currents from the same presynaptic population. Pharmacological studies verified that these currents were mediated by GABAA and AMPA/NMDA receptors, consistent with functional co-release of GABA and glutamate. Ongoing studies are characterizing the in vivo activity and function of this co-releasing cortical neuronal population in behaving mice. Together, these studies identify a unique cortical interneuron population with dual-transmitter capacity and suggest that it contributes to local auditory cortical signaling through mixed GABAergic and glutamatergic synaptic transmission.

Disclosures: L.G. Vattino: None. **S. Pak:** None. **C. MacGregor:** None. **B. Wu:** None. **H. Sohn:** None. **D.B. Arnold:** None. **A.E. Takesian:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.13/K7

Topic: B.04. Synaptic Transmission

Support: UIC Campus Research Board Award

Title: Voluntary versus forced pre-Ischemic exercise: differential BDNF-mediated neuroprotection in hippocampus

Authors: *B. HEIT[1], C. HECKMAN[2];
[1]Neurosci., [2]Dept. of Neurosci., Northwestern Univ., Chicago, IL

Abstract: Cerebral ischemia induces a rapid cascade of cellular reactions due to energy depletion which triggers neuronal death within minutes of an occlusion. The severity of this early sequela is a powerful determinant of neurological outcome. Given the unpredictability of stroke and the fulminant cellular damage that ensues, post-stroke therapies provide limited effectiveness. Thus, there is vital need for preparative interventions that prevent and/or reduce the severity of ischemic events. Exercise is one promising intervention: regular physical activity decreases stroke incidence and mitigates ischemic damage in both humans and animals. Nonetheless, the mechanisms by which pre-ischemic exercise protects neurons from ischemia are poorly understood, and the efficacy of *volitional* versus *forced* exercise remains debated. One remarkable response to exercise is the robust release of brain-derived neurotrophic factor (BDNF) throughout the nervous system, most notably, in hippocampus. Importantly, stroke pathogenesis can be reproduced in slices of murine hippocampi *in vitro* by transient removal of the oxygen supply. Here, hippocampal slices were prepared from three groups of mice: sedentary controls, mice given six weeks of voluntary wheel running, and mice subjected to six weeks of forced treadmill running. Slices were assessed for three measures of ischemic sensitivity: the latency to anoxic depolarization (AD) following total O_2 deprivation, the magnitude of recovery upon reoxygenation after 2 min in the depolarized state, and the sensitivity of synaptic transmission to mild hypoxia ($25\%O_2/75\%N_2$). Immunohistochemistry was also performed on hippocampal tissue to reveal whether running-induced neuroprotection correlates with enhanced BNDF expression. When compared to sedentary controls, both voluntary and forced pre-ischemic running lengthened AD latency, enhanced recovery after AD, and mitigated synaptic suppression during mild hypoxia. These effects were strongly correlated with exercise-mediated upregulation of BDNF in hippocampal tissue. Interestingly, forced running uniquely produced decreased irreversible cellular damage, decreased suppression of synaptic transmission during hypoxia, and NMDAR-mediated post-hypoxic potentiation when compared to sedentary mice and wheel-running mice. Moreover, our early findings suggest that chronic *in vivo* administration of BDNF/TrkB antagonist, ANA-212, dampens these neuroprotective effects. Collectively, these data explicate the running-induced and BDNF-mediated permutations to the biophysical properties of neurons which promote prophylaxis during early-onset stroke.

Disclosures: B. Heit: None. **C. Heckman:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.14/K8

Topic: B.04. Synaptic Transmission

Support: NIH Grant R35 GM138023
NIH Grant T32 AG052375

NIH Grant T32 GM133369
NSF Cooperative Agreement No. OIA-2242771

Title: The Roles of Endogenous Zinc in GABAergic Neurotransmission in the Mouse Auditory Cortex

Authors: *K. BAINER, R. RUBY, E. TRATE, C. T. ANDERSON;
Dept. of Neurosci., West Virginia Univ., Morgantown, WV

Abstract: Synaptic zinc (as Zn^{2+}) is a powerful neuromodulator that is highly enriched within the brain, specifically in the cortex, hippocampus, amygdala, and striatum. Synaptic zinc in the brain is ZnT3 dependent. ZnT3 is a zinc transporter protein that packages zinc into synaptic vesicles to be co-released with other neurotransmitters. The auditory cortex, which is crucial for higher sound processing, contains cells enriched with synaptic zinc. Glutamatergic neurons in the auditory cortex express ZnT3 that colocalizes with VGLUT1, allowing synaptic zinc to be co-released with glutamate. More recent evidence has shown ZnT3 mRNA is also expressed in two populations of inhibitory neurons in the auditory cortex: Somatostatin (SOM) and Parvalbumin-positive (PV) cells, suggesting that endogenous zinc has functional consequences on inhibitory singling through GABA receptor modulation. Understanding the roles that synaptic zinc plays in modulation of inhibition is crucial to understanding normal neuronal processing.We performed stereotaxic injections of flex-AAVs encoding the excitatory opsin ChrimsonR or Chronos into the auditory cortex of Cre-driver mouse lines, to express the opsins in SOM and PV inhibitory neurons. We also injected a retrograde tracer of cholera toxin into the inferior colliculus to label corticocollicular neurons. We made acute brain slices of the auditory cortex and performed whole-cell patch-clamp recordings of labeled layer 5 corticocollicular neurons. We recorded spontaneous and optogenetically stimulated GABA responses from corticocollicular cells and determined the roles of synaptic zinc on inhibitory neurotransmission using pharmacological and genetic approaches. Inhibitory neurons are crucial for normal neuronal processing because they refine and shape the tuning of excitatory neurons. Here we expand the known roles for synaptic zinc release from inhibitory neurons and describe novel effects of zinc on shaping inhibitory signaling in the cortex.

Disclosures: K. Bainer: None. **R. Ruby:** None. **E. Trate:** None. **C.T. Anderson:** None.

Poster

PSTR214: Pre- and Postsynaptic Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR214.15/L1

Topic: B.04. Synaptic Transmission

Support: NIH Grant DC004274

Title: Asymmetric metabolic requirements for IPSCs and EPSCs at auditory synapses

Authors: *A. DAGOSTIN[1], H. P. VON GERSDORFF[2];
[1]OHSU, Portland, OR; [2]Vollum Inst., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Energy availability is a critical determinant of neural circuit function. The brain's dependence on continuous metabolic substrate supply is underscored by the rapid onset of synaptic failure during hypoxia and the cognitive deficits that precede measurable ATP depletion in hypoglycemic states. The presynaptic terminal is a particularly demanding compartment, where the majority of ATP is thought to be derived from mitochondrial oxidative phosphorylation (OxPhos). Emerging evidence suggests, however, that glycolysis and OxPhos may not contribute equally to all aspects of synaptic function, and that the relative pathway dependence varies across synapse identity and stimulation demands. Here we examined how graded metabolic challenges affect excitatory and inhibitory synaptic transmission in principal neurons of the Lateral Superior Olive (LSO) in mature (>P30) CBA/CaJ mice. Patch-clamp electrophysiology was performed on auditory brainstem slices (250 μm) to record membrane properties and synaptic currents from LSO principal neurons under high-frequency stimulation (HFS, 100 Hz), eliciting glycinergic IPSCs and glutamatergic EPSCs via afferent fiber stimulation. Extracellular glucose was first reduced from 10 mM to 1 mM, attenuating the amplitude of both IPSCs and EPSCs. Subsequent inhibition of mitochondrial ATP synthase (Complex V) with oligomycin (5 μM) further reduced initial and steady-state current amplitudes during HFS trains, while short-term synaptic depression fraction and recovery remained unaffected. Notably, IPSC amplitude showed greater sensitivity to glucose restriction than EPSCs, indicating that glycinergic transmission is more vulnerable to changes in glucose availability. Complete glycolytic blockade via 2-deoxyglucose (2-DG) hyperpolarized the resting membrane potential and reduced postsynaptic currents within about five minutes of treatment. Together, these results suggest that glycolysis alone can partially sustain synaptic transmission in both inhibitory and excitatory LSO pathways when OxPhos is severely compromised. Nevertheless, the greater sensitivity of glycinergic synapses to glucose restriction suggests that inhibitory transmission carries a higher intrinsic energy demand, with important implications for understanding how metabolic stress differentially disrupts the E/I (excitation-inhibition) balance in brain circuits.

Disclosures: A. Dagostin: None. **H.P. von Gersdorff:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.01/L2

Topic: B.05. Synaptic Plasticity

Support: NIMH Grant MH118298 (WX)
NIMH Grant MH131717 (WX)

Title: C-terminal dephosphorylation of GluN2A accelerates NMDAR current kinetics in a PP2B-dependent manner

Authors: *A. ETINGOF[1], W. XU[2];
[2]Neurosci., [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: NMDA receptor (NMDAR)-dependent synaptic plasticity is a key cellular substrate for learning and memory formation. Mutations in genes involved in glutamatergic synaptic transmission and plasticity, including *GRIN2A* and *NRGN*, have been identified in schizophrenia and autism spectrum disorder (ASD), implicating this pathway in the pathophysiology of these disorders. NMDAR-mediated calcium (Ca) influx drives a Ca/calmodulin (CaM)-dependent signaling cascade essential for synaptic plasticity. Neurogranin (Ng), encoded by *NRGN*, regulates CaM availability. Our previous studies showed Ng knockdown accelerates NMDAR current kinetics and impairs LTP at hippocampal Schaffer collateral-CA1 synapses via increased protein phosphatase 2B (PP2B) activity. Four C-terminal serine residues in the NMDAR subunit GluN2A, encoded by the gene *GRIN2A*, were identified as hypophosphorylated with Ng knockdown (Hwang et al., 2021), implicating the Ng-PP2B-GluN2A axis in regulation of NMDAR current kinetics. However, whether PP2B directly targets GluN2A at these loci remains unclear. Here, we used an *in vitro* artificial synapse model in HEK293T cell-mouse cortical neuron coculture to examine the effect of four GluN2A phosphosites on NMDAR decay kinetics. Artificial synapse formation was validated by immunohistochemistry. Electrophysiological recordings were obtained from HEK293T cells expressing GluN1 and either wild-type (WT) or phospho-mutant (S4A) GluN2A. Decay kinetics of neural activity-evoked EPSCs were compared between variants. S4A GluN2A-containing NMDARs had significantly accelerated decay kinetics when compared to WT GluN2A-containing NMDARs (p=0.0031, unpaired t-test). To examine whether the difference in decay kinetics between cells expressing WT and S4A GluN2A were due to PP2B activity, we co-expressed constitutively active PP2B (CNCA) in the HEK293T cell, or a phospho-dead PP2B (CNPD) as a control. Two-way ANOVA (GluN2A genotype × PP2B variant) revealed a significant interaction ($F(1,18) = 12.61$, $p = 0.0023$); Tukey's post hoc tests showed that decay kinetics of WT NMDARs were accelerated ($p = 0.0002$), while the S4A mutation occluded the acceleration of decay kinetics with CNCA co-expression ($p = 0.8452$). These results indicate that increased PP2B activity led to the acceleration of decay kinetics in WT NMDARs by dephosphorylation of the four phosphosites in the GluN2A C-terminus and suggest that dysregulation of the Ng-PP2B-GluN2A pathway may play a role in NMDAR-dependent plasticity deficits relevant in schizophrenia and ASD.

Disclosures: A. Etingof: None. **W. Xu:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.02/L3

Topic: B.05. Synaptic Plasticity

Support: NSF-IOS 2224262

Title: Wnt5a acutely reshapes the dendritic phosphoinositide landscape through a phospholipase C-dependent mechanism

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Abstract: Phosphoinositides are central regulators of neuronal membrane physiology. Plasma-membrane phosphatidylinositol 4,5-bisphosphate (PIP2) modulates HCN and KCNQ channels and serves as a substrate for both phospholipase C (PLC) and phosphoinositide 3-kinase (PI3K). PLC hydrolyzes PIP2 to generate inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), while PI3K converts PIP2 into phosphatidylinositol 3,4,5-trisphosphate (PIP3). Thus, PLC-mediated PIP2 turnover could acutely affect neuronal signaling through IP3/DAG production and PIP2 depletion, while also modulating PI3K-dependent PIP3 production, a lipid signal implicated in AMPA receptor clustering and synaptic strength. Wnt5a, a noncanonical Wnt ligand, regulates spine morphogenesis, NMDA receptor-mediated synaptic transmission, and neuronal excitability through a PLC-dependent mechanism consistent with regulation of phosphoinositide metabolism. However, how Wnt5a couples to phosphoinositide turnover and reshapes neuronal lipids remains undefined. Using FRET biosensors in HEK293 cells and hippocampal neurons, we mapped a receptor-to-lipid cascade. In HEK293 cells, Wnt5a drove sustained IP3 production (LIBRAvII sensor) that required receptor tyrosine kinase-like orphan receptor 2 (ROR2) and was abolished by PLC inhibition. This required Frizzled co-receptors, as Wnt5a failed to induce IP3 production in HEK293 cells lacking endogenous Frizzled receptors. Chemically induced ROR2 homodimerization also failed to induce IP3 production. These data suggest productive signaling requires a ligand-induced ROR2/Frizzled complex rather than ROR2 homodimers. The extracellular cysteine-rich domain and intracellular C-terminal region of ROR2 were required for efficient signaling. In neurons, Wnt5a triggered PLC-dependent IP3 production in dendrites with a second-scale onset. Lipid FRET measurements revealed sustained, non-recovering depletion of PIP2 (PlcR sensor) together with a transient reduction in PIP3 (InPAkt sensor), reaching a minimum within ~15 s before partly recovering despite continued PIP2 depletion. All lipid responses were eliminated by PLC inhibition. This signature indicates maintained, not transient, PLC activity, with the PIP3 pool acutely sensitive to substrate depletion. These findings define a Wnt5a-PLC pathway that acutely reshapes the dendritic phosphoinositide landscape, providing a proximal mechanism for regulating ion-channel function and intrinsic neuronal properties. Our results identify dendritic phosphoinositides as a target through which Wnt signaling could tune synaptic and neuronal properties.

Disclosures: N.N. Foressi: None. **A. Barria:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.03/L4

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01MH107615
Veterans Affairs Merit Awards 101BX004062, 101BX003631, 101BX006018
MPower Early Scholars Investment Fund

Title: Corticotropin-releasing factor selectively augments the synaptic effects of ketamine metabolite via protein kinase C signaling

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Abstract: Background/Objectives: Major depressive disorder (MDD) is associated with structural and functional alterations in mood-regulating brain regions, including the hippocampus. Depression and its accompanying cognitive deficits are linked to reduced synaptic strength at key hippocampal excitatory synapses, such as the stress-sensitive entorhinal cortex (EC) temporoammonic (TA) to CA1(TA-CA1), Schaffer collateral-CA1, and perforant path (PP)-GC synapses. The rapid-onset antidepressant ketamine, and its bioactive metabolite (2R,6R)-hydroxynorketamine (2R6R)), strengthen excitatory synaptic transmission. However, the specific synapses targeted by 2R6R, the mediators underlying any differential synaptic effects, and 2R6R's mechanisms of action are not fully understood. In this study, we investigated the mechanisms underlying how the stress hormone, corticotropin-releasing factor (CRF) enhances the synaptic effects of 2R6R at hippocampal synapses.**Methods:** 9 to 12-week-old male and female C57BL/6J mice were used. We combined electrophysiological recordings of field excitatory postsynaptic potentials with pharmacological approaches in mouse hippocampal slices to investigate the effects of 2R6R alone and the combination of 2R6R and CRF on synaptic transmission at hippocampal synapses.**Results:** HNK exerts a synapse-specific effect at the hippocampal synapses. A combination of CRF and HNK potentiated TA-CA1, but not PP-GC synapse. Inhibition of CRF receptor 1, but not 2, blocked CRF/HNK-induced potentiation, indicating a specific receptor involvement. Additionally, PLC/DAG/PKC signaling is essential for CRF/HNK-mediated potentiation at the TA-CA1 synapse. CRF/HNK enhances long-term potentiation (LTP) and reduces long-term depression (LTD) at the TA-CA1 synapse. Notably, inhibition of PKC blocks CRF/HNK-mediated LTP at the TA-CA1 synapse.**Discussion:** These experiments revealed a synapse-specific function of CRF in enhancing the synaptic effect of 2R6R in the hippocampus, therefore, providing a novel insight into our understanding of the potential synaptic mechanisms by which 2R6R may exert its rapid-onset antidepressant effect. Approaches combining manipulations that acutely increase CRF combined with ketamine and/or 2R6R may have utility in the treatment of depression

Disclosures: M.I. Ajibola: None. **K.A. Brown:** None. **P. Georgiou:** None. **T.D. Gould:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-author in Patents related to (2R,6R)-HNK.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.04/L5

Topic: B.05. Synaptic Plasticity

Support: NIH/NIDA R01 DA056113

Title: Estradiol Signalling Pathways Mediating Sex Differences In Striatal Synaptic Plasticity

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Abstract: Sex differences are observed in reward learning, habit formation and addiction related behavior in rodents and humans. The striatum is central to reward learning and in previous work we showed that estradiol impairs synaptic long term potentiation (LTP) in the dorsomedial striatum. To identify the molecular pathways involved in estradiol-mediated impairment of LTP, we developed a multi-compartmental D1 Spiny Projection Neuron signaling pathway model using NeuroRD, a computationally-efficient stochastic reaction-diffusion simulator. Synaptic inputs included glutamate activation of Gq coupled pathways, dopamine activation of Gs coupled pathways and calcium activation of calmodulin dependent pathways. The model output was the change in Extracellular signal-Regulated Kinase 1/2 (ERK), a key integrator of signaling pathways involved in synaptic plasticity and memory formation. To investigate the effect of estradiol, we simulated the response to the LTP induction protocol known as Theta Burst Stimulation (TBS), with and without the activation of G-Protein coupled Estrogen Receptor (GPER) via the Gs pathways and Estrogen Receptor alpha (ERα) via the Gq pathways. TBS alone produced a two-fold increase in phospho-ERK that persisted for approximately 10 minutes. Activation of GPER with 5 nM estradiol produced a 10-fold increase in basal cAMP (as shown experimentally), resulting in a three-fold increase in phospho-ERK in both spine and dendrite. This increase was mediated by two distinct pathways: reduced activity of Striatum Enriched Protein tyrosine phosphatase (STEP) and enhanced activation of ERK by upstream kinases. Activation of ERα with 5 nM estradiol led to a rapid transient increase in Inositol Triphosphate (IP3) lasting about 5 minutes (as shown experimentally) and 2-arachidonylglycerol (an endocannabinoid that drives Long Term Depression). Our main result shows that, in the presence of 5nM estradiol, TBS produced only a minimal increase in phospho-ERK in both spine and dendrite. These results suggest that the increased basal activation of phospho-ERK due to estradiol reduces the dynamic range of ERK, making it less sensitive to TBS, providing a potential molecular mechanism for sex differences in reward learning.

Disclosures: V. mallya: None. **K.L. Blackwell:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.05/L6

Topic: B.05. Synaptic Plasticity

Support: NIH 1T32GM156537
NIH 1R01NS102239

Title: Slack regulates cytoskeletal breakdown during developmental long-term potentiation

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Abstract: Slack (also known as KCNT1 or KNa1.1) is a sodium-activated potassium channel expressed in neurons throughout the brain. The cytoplasmic domain of Slack binds several signaling proteins including regulators of translation and Phactr1, a Protein Phosphatase 1 (PP1) interacting protein. Previous work has indicated that activation of Slack channels releases Phactr1 and PP1 from the channel complex. In humans, gain-of-function mutations lead to profound early-onset intellectual disability and epilepsy with no approved disease-modifying treatments. Deletion of the gene encoding Slack in mice leads to complete loss of long-term potentiation (LTP) and metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD) at the CA1 synapse in the developing hippocampus. A key feature of both LTP and mGluR-LTD in the developing hippocampus is the rapid and transient breakdown of the actin-rich cytoskeleton. This process requires the rapid activation of the actin-regulatory protein cofilin. Both processes also include the cleavage of spectrin αII, likely to allow for diffusion of key proteins in and out of the spine. We have now found that hippocampal neurons from Slack-/- neurons have higher levels of activated cofilin and increased cleavage of spectrin αII. Furthermore, loss of Slack prevents the inactivation of cofilin during LTP and does not further cleave spectrin αII. In contrast, blocking Slack in wild-type mice prevents the activation of cofilin and the cleavage of spectrin αII during LTP. We hypothesize that these effects result from the interaction of Slack with Phactr1, which provides substrate specificity for PP1 to dephosphorylate both cofilin and spectrin αII. Specifically, loss of Slack would be expected to prevent sequestration of Phactr1/PP1 to the channel complex, making it constitutively active. Blocking Slack channels may prevent the release of PP1. Our results suggest that Slack acts as a key regulator of cytoskeletal breakdown during developmental synaptic plasticity.

Disclosures: S. Gilliat: None. **J. Wu:** None. **L.K. Kaczmarek:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.06/L7

Topic: B.05. Synaptic Plasticity

Title: Group II metabotropic glutamate receptors and CD38 contribute to lactate-induced potentiation of NMDA receptor currents

Authors: *G. HERRERA-LÓPEZ[1], H. FIUMELLI[2], P. J. MAGISTRETTI[3];
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Abstract: Lactate, long considered primarily an energy substrate supplied by astrocytes, is increasingly recognized as a signaling molecule that modulates synaptic transmission, plasticity, and memory. We recently showed that lactate potentiates NMDA receptor (NMDAR) currents through a redox-sensitive mechanism involving GluN2B-containing receptors. Here, we identify a complementary signaling pathway that contributes to lactate-induced potentiation of NMDAR function in primary cortical neurons. Whole-cell patch-clamp recordings showed that lactate strongly enhanced NMDAR currents evoked by glutamate. In contrast, its effect was much smaller when NMDA was used as the agonist, implicating a role for non-NMDA glutamate receptors. Consistent with this idea, pharmacological blockade of group II mGluRs (mGluRII), but not group I mGluRs, prevented the effect of lactate. Conversely, co-application of the selective mGluRII agonist DCG-IV with NMDA reproduced the full potentiation observed with glutamate in the presence of lactate. We next identified downstream components of this pathway. Pharmacological inhibition showed that lactate-induced potentiation requires Gi/o signaling, PI3K, and PKC. Inhibition of PKCα/β abolished the effect of lactate, and western blot analysis showed that lactate increased PKCα/β phosphorylation downstream of mGluRII activation. Because PKCα/β are Ca^{2+}-dependent isoforms, we investigated intracellular Ca^{2+} dynamics. Lactate induced Ca^{2+} elevations independently of NMDAR activation. Inhibition of CD38, a redox-sensitive enzymatic complex involved in intracellular Ca^{2+} mobilization, prevented both NMDAR potentiation and PKCα/β phosphorylation. These findings identify a new signaling pathway by which lactate potentiates NMDAR function. Taken together with our previous work, these findings suggest that lactate acts through convergent redox- and mGluRII-dependent mechanisms involving CD38-mediated Ca^{2+} signaling and PKC activation. These mechanisms provide a cellular link between astrocyte-neuron metabolic coupling and the modulation of synaptic plasticity.

Disclosures: G. Herrera-López: None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.07/L8

Topic: B.05. Synaptic Plasticity

Support: NIH Grant NS084111
NIH Grant NS114914
NIH Grant NS119512

Title: Scaffolding Synaptic Plasticity: Scribble Couples Actin Remodeling with AMPAR Trafficking During LTD

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Abstract: Synaptic plasticity refers to the brain's capacity to adapt and refine its function in response to external input. This adaptability depends on a tightly regulated balance of communication at synapses, specialized points of contact between neurons. Such communication is mediated largely by ionotropic glutamate receptors, specifically AMPA receptors (AMPARs), through which changes in synaptic strength are governed by the regulated insertion and removal of AMPARs at the postsynaptic membrane. Within this framework, long-term depression (LTD) represents a form of synaptic plasticity in which synaptic strength is reduced through the activity-dependent removal of AMPARs, a mechanism essential for learning, memory refinement, and flexible behavior. This process necessitates the coordinated integration of cytoskeletal remodeling and receptor endocytic trafficking, yet the molecular scaffolds that spatially and temporally organize these events remain incompletely defined. Here, we identify the polarity protein Scribble as a critical orchestrator of AMPAR endocytosis during LTD.We biochemically demonstrate that Scribble assembles a signaling complex with the clathrin adaptor AP2, the Rac1 guanine nucleotide exchange factor Prex1, and its upstream LTD-associated regulator PP1α. Through these interactions, Scribble coordinates a two-pronged mechanism that couples AMPAR internalization and post-endocytic trafficking with actin cytoskeletal remodeling. Association with AP2, together with Scribble enrichment at clathrin-coated structures and near endocytic machinery in dendrites, supports a role in receptor internalization and subsequent sorting. In parallel, interaction with PP1α and Prex1, along with disruption of Rac1 activity following Scribble knockdown, links Scribble-dependent signaling to the actin remodeling required for efficient receptor removal. Consistent with this model, live imaging of SEP-GluA2 reveals that NMDA-induced AMPAR internalization is impaired following Scribble knockdown. At the physiological level, Scribble knockdown abolishes LTD in acute hippocampal slices, as demonstrated via electrophysiology recordings. Together, our findings establish Scribble as a molecular scaffold linking Rac1 signaling to endocytic trafficking to drive AMPAR removal during LTD and integrate synaptic plasticity across molecular, cellular, and circuit levels.

Disclosures: T.A. Khan: None. **L. Cancedda:** None. **M. Shelly:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.08/M1

Topic: B.05. Synaptic Plasticity

Support: NS125271
MH019524
NS086750

Title: Coordination of CaMKII binding at NMDARs and L-Type Calcium Channels Supports Excitation-Transcription Coupling

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Abstract: Calcium/calmodulin-dependent kinase II (CaMKII) is a brain-abundant protein activated by Ca^{2+} which plays a key role in synaptic plasticity, learning and memory. During synaptic stimulation, CaMKII accumulates in excitatory synapses to support downstream signaling required for long-term potentiation (LTP) or behavior timescale plasticity (BTSP). This includes the critical process of Excitation-Transcription Coupling (E-TC). Recent research explores CaMKII's "structural" role, where interactions with synaptic proteins facilitate LTP along with or instead of enzymatic activity. Our work began with CaMKII interactions with the C-terminal domain of N-methyl-d-aspartate receptor (NMDAR) subunit GluN2B, whose mutation to prevent CaMKII binding impairs LTP. However, NMDARs are not the only CaMKII binding partner in dendritic spines. Ca_V1 L-type voltage gated Ca^{2+} channels (LTCCs) also bind to CaMKII on their N-terminal domain (NTD), contribute to CaMKII translocation and LTP, and show impaired E-TC when mutated to abolish CaMKII binding. Using Fluorescence Lifetime Imaging Microscopy to measure Förster Resonance Energy Transfer (FRET-FLIM), we directly monitor interactions between CaMKII and either LTCCs or NMDARs. We find that the interaction of CaMKII with the CaV1-NTD is similar in extent to the GluN2B C-terminal domain. The respective interactions are abolished by modification of key residues within their CaMKII binding domains (GluN2B LRS or $Ca_V1.2$ RKR/AAA). Moreover, fluorescently untagged Ca_V1-NTD competes with GluN2B-CTD for CaMKII binding in an RKR-sensitive manner. We study the interplay between these CaMKII binding interactions in dendritic spines using immunocytochemical monitoring of pCaMKII puncta in cortical neurons exposed to NMDA+Cd, which drives NMDAR opening without LTCC flux. The longevity of pCaMKII in dendritic spines is abbreviated when LTCC gating is blocked with nimodipine. Furthermore, nimodipine alters the dynamics of GluN2B-CTD phosphorylation at Ser1303 within the LRS locus. We are testing a scenario that features a molecular handoff of CaMKII from GluN2B-CTD to Ca_V1-NTD, facilitated by Ser1303 phosphorylation. This would enable convergence of glutamate signals that activate NMDARs and depolarization that triggers LTCCs, appropriate to support E-T coupling and BTSP.

Disclosures: H.G. Khaled: None. **V. Jain:** None. **X. Wang:** None. **B. Schuman:** None. **R.W. Tsien:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.09/M2

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI 23K06344

Title: Rational engineering of a multiplex fluorescent imaging platform to unravel temporal integration of calcium-calcineurin signaling in intact neural circuits

Authors: *H. FUJII[1], K. OTA[2], Y. KONDO[2], H. SONG[2], M. OKAMURA[2], H. KONDO[2], H. BITO[2];
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Abstract: Understanding how neuronal activity is translated into intracellular biochemical signaling is a central challenge in neuroscience. Among these signals, calcineurin (CaN) is a Ca^{2+}/calmodulin-dependent phosphatase that regulates synaptic strength across multiple time scales. Despite its fundamental importance, how CaN activity is dynamically regulated at the single-cell and subcellular levels in intact neural circuits has remained elusive.
Using dFOMA (Dual-FRET imaging with Optical MAnipulation), a multiplex FRET imaging platform with localized photostimulation, we previously found that similar total amounts of CaN activity were evoked by both low- and high-frequency stimulation regimes, suggesting that CaN might act as a biochemical integrator of repeated neuronal inputs. However, a quantitative view of CaN signaling dynamics in intact neurons and intact neural circuits is still lacking. To address these limitations, we here report the rational engineering of a multiplex fluorescent imaging platform and the development of new generations of fluorescent indicators.
We first established dFOMA2, an improved platform with enhanced indicator specificity and sensitivity. By combining dFOMA2 with a newly developed blue Ca^{2+} indicator, we achieved fast, four-channel multiplex imaging of Ca^{2+}, CaN, CaMKII, and neuronal morphology at sub-second resolution. This approach revealed quantitatively distinct rise and decay kinetics of Ca^{2+}, CaN, and CaMKII, indicating three distinct temporal domains of calcium-dependent signaling dynamics in cultured neurons. Finally, we developed a novel CaN indicator suitable for in vivo two-photon imaging and simultaneously monitored Ca^{2+} and CaN dynamics in layer 2/3 cortical neurons. We found that CaN activity did not simply follow individual Ca^{2+} transients, but showed slower decay kinetics, allowing closely spaced Ca^{2+} events to be temporally summed on a subsecond-to-second time scale.
Together, these results provide a multiplex imaging framework for dissecting how neuronal activity is decoded by downstream effectors with distinct temporal filtering properties, and reveal that CaN functions as a short-timescale biochemical integrator of neuronal Ca^{2+} activity in intact neural circuits.

Disclosures: H. Fujii: None. **K. Ota:** None. **Y. Kondo:** None. **H. Song:** None. **M. Okamura:** None. **H. Kondo:** None. **H. Bito:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.10/M3

Topic: B.05. Synaptic Plasticity

Support: R37 MH057068
R01 MH115304

Title: Sevoflurane primes PKMζ for hippocampal synaptic tagging: Implications for postoperative cognitive dysfunction

Authors: *P. TSOKAS[1], K. D. ALLEN[7], L. M. RODRIGUEZ VALENCIA[2], D. A. CANO[3], C. HSIEH[4], K. NI[3], E. KAUR[3], M. DESAI[8], I. M. LAMBERT[3], H. J. SMITH[4], K. KAMALAKAR[4], A. SMITH[4], A. A. FENTON[9], I. S. KASS[5], J. E. COTTRELL[2], T. C. SACKTOR[6];
[1]Pathology; Physiology&Pharmacology; Anesthesiology; RF Furchgott Ctr. for Neural & Behavioral Sci., [2]Anesthesiol., [3]Sch. of Med., [4]Physiol. & Pharmacology; RF Furchgott Ctr. for Neural & Behavioral Sci., [5]Physiology&Pharmacology; Anesthesiology; RF Furchgott Ctr. for Neural & Behavioral Sci., [6]Physiology&Pharmacology; Neurology; Anesthesiology; RF Furchgott Ctr. for Neural & Behavioral Sci., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [7]Ctr. for Neurosci. and Behavior, Medgar Evers College,, Brooklyn, NY; [8]Oakland Univ. William Beaumont Sch. of Med., Royal Oak, MI; [9]New York Univ., New York, NY

Abstract: Sevoflurane produces amnesia during anesthesia and may also cause long-lasting cognitive impairment, such as postoperative cognitive dysfunction (POCD). This persistent adverse outcome suggests that sevoflurane may interfere with the core molecular processes involved in the formation and maintenance of long-term memory. The biological basis of long-term memory is thought to be late-phase long-term potentiation (late-LTP), which depends on two key processes: 1) the new synthesis of plasticity-related proteins — notably the persistently active protein kinase C isoform PKMζ, which increases synaptic strength — and 2) synaptic tagging, whereby the newly synthesized proteins are targeted to activated synapses. Our findings show that brief sevoflurane exposure elevates PKMζ levels in the hippocampal CA1 region of both mice and rats, *in vivo* as well as in brain slices. However, sevoflurane-induced PKMζ differs from that produced by LTP: it accumulates in neuronal cell bodies rather than dendrites, lacks activation-loop phosphorylation (therefore kinase activity), and is not associated with upregulation of its synaptic tag KIBRA, or increased synaptic strength. This indicates that sevoflurane triggers PKMζ synthesis without activating synaptic tagging. To explore the consequences of this synthesis, we tested subthreshold synaptic stimulation — strong enough to produce transient synaptic tags and early-LTP, but not sufficient to drive the protein synthesis required for late-LTP. When applied within an approximately one-hour window before or after sevoflurane exposure, this weak stimulation was capable of inducing late-LTP. This demonstrates that volatile anesthetics can prime hippocampal circuits for lasting changes in synaptic strength. PKMζ-priming reveals a potentially pathological mechanism whereby aberrant hippocampal activity triggers random synaptic tagging within a critical time window around anesthesia. This introduction of non-specific LTP into hippocampal networks potentially provides a model for POCD.

Disclosures: P. Tsokas: None. **K.D. Allen:** None. **L.M. Rodriguez valencia:** None. **D.A. Cano:** None. **C. Hsieh:** None. **K. Ni:** None. **E. Kaur:** None. **M. Desai:** None. **I.M. Lambert:** None. **H.J. Smith:** None. **K. Kamalakar:** None. **A. Smith:** None. **A.A. Fenton:** None. **I.S. Kass:** None. **J.E. Cottrell:** None. **T.C. Sacktor:** None.

Poster

PSTR215: Synaptic Plasticity: Kinases, Phosphatases, and Intracellular Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR215.11/M4

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R37 MH057068
NIH Grant R01 MH115304
NIH Grant R01 NS105472
NIH Grant R01 MH132204

Title: PKMζ-KIBRA interactions, molecular turnover, and memory

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Abstract: How can the molecules that strengthen synaptic connections maintain memory in the face of molecular turnover? Our previous work showed that persistent interaction between the postsynaptic scaffolding protein, KIBRA, and the autonomously active PKC isoform, PKMζ, is crucial for maintaining synaptic long-term potentiation (LTP) and memory lasting at least a month. This duration is longer than the lifespans of individual KIBRA and PKMζ molecules. Biophysical modeling of the interaction suggests oligomers of KIBRA-PKMζ dimers, but not individual dimers or monomers, can overcome molecular turnover by continuously incorporating newly synthesized KIBRA and PKMζ, replacing those that have degraded. Here we used AlphaFold 3 to predict the structures of KIBRA-PKMζ heterodimers and heterohexamers and to examine the sites of action of two different inhibitors of KIBRA-PKMζ interaction that disrupt established late-LTP and long-term memory. The structures predict that the peptide K-ZAP blocks formation of heterodimers, whereas the small molecule ζ-stat prevents PKMζ of one heterodimer from binding a second KIBRA and PKMζ, essential for forming larger oligomeric structures. We show that ζ-stat, like K-ZAP, disrupts 1-month-old spatial memory. Thus, continuous formation of KIBRA-PKMζ oligomers can be a core molecular mechanism driving the persistence of long-term memory in the face of molecular turnover.

Disclosures: C. Hsieh: None. **D.A. Cano:** None. **P. Tsokas:** None. **J.E. Cottrell:** None. **A.A. Fenton:** None. **H.Z. Shouval:** None. **T.C. Sacktor:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.01/N1

Topic: B.09. Glial Mechanisms

Support: NIH NINDS Grant 5KO1NS110981-06
AAUW American Fellowship

Title: Norepinephrine signaling primes astrocytic mGluR3 activation via α1-adrenergic receptor

Authors: *E. BALBUENA[1], S. CHITTARANJAN[2], A. ROSZCZYK[1], T. BUBEL[1], N. A. SMITH[1];
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Abstract: Norepinephrine (NE) is a neurotransmitter released from the locus coeruleus (LC) in the brain that is significant for regulating neuronal synaptic plasticity and transmission. However, it is unknown whether NE affects local synaptic plasticity and transmission directly or through glial mediated responses, and to what extent LC-NE can modulate local glial neuronal communication. Astrocytes, the most abundant glial cells in the brain, are strategically positioned to receive LC-NE input. They express both adrenergic and metabotropic glutamate receptors, each of which has been implicated in synaptic plasticity. Here, we aimed to investigate whether NE signaling can prime astrocytes to respond to local glutamatergic activity via the predominantly expressed astrocytic metabotropic glutamate receptor 3 (mGluR3). We hypothesized that astrocytic Ca^{2+} signaling evoked by local mGluR3 activation would be enhanced following α1-adrenergic receptor (α1-AR) priming. To test this, we used a GCaMP5GtdTm/ Aldh1l1-creER transgenic mouse line to visualize astrocyte morphology and Ca^{2+} signals, combined with pharmacology and 2-photon microscopy to monitor Ca^{2+} dynamics ex vivo in cortical astrocytes. We first applied the mGluR2/3 agonist LY354740 via picospritzer to measure astrocyte Ca^{2+} responses in the somatosensory cortex. Slices were bathed in ACSF containing either tetrodotoxin (TTX) alone (n=6, aged 4-10 weeks), or mGluR2/3 antagonist LY341495 plus TTX (n=6, aged 4-10 weeks). Our data indicate that glutamate triggers intracellular Ca^{2+} release in astrocytes via mGluR3, and that this response is ameliorated by mGluR3 inhibition. We next tested evoked Ca^{2+} signaling to LY354740 in the presence of ACSF containing either TTX alone (n=6, aged 4-10 weeks), or phenylephrine (α1-AR agonist) plus TTX (n=6, aged 4-10 weeks). Our data indicate that α1-AR activation primes astrocytes for faster intracellular Ca^{2+} responses via mGluR3. In contrast, this α1-AR-mediated priming is reduced in the presence of the α1-AR antagonist terazosin (n=6, aged 4-10 weeks). These findings reveal a novel mechanism by which NE can regulate astrocyte responses to local

glutamatergic signaling, thereby giving them the potential to ultimately modulate synaptic plasticity. This work advances our understanding of NE-mediated glial-neuronal communication and its potential relevance to brain health and disease.

Disclosures: E. Balbuena: None. **S. Chittaranjan:** None. **A. Roszczyk:** None. **T. Bubel:** None. **N.A. Smith:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.02/N2

Topic: B.09. Glial Mechanisms

Title: Adrenergic receptor family-specific astrocyte signaling differentially modulates hippocampal CA1 input pathways

Authors: *J. KIM, C. EROGLU;
Duke Univ., Durham, NC

Abstract: Astrocytes regulate synaptic transmission, but whether astrocyte neuromodulatory functions are specialized according to the local circuit pathways they contact remains poorly understood. Hippocampal CA1 receives two major excitatory inputs in distinct layers: Schaffer collateral (SC) input from CA3 to stratum radiatum (SR) and temporoammonic (TA) input from entorhinal cortex layer III to stratum lacunosum-moleculare (SLM). We hypothesized that distinct adrenergic receptor families recruit layer-specific astrocyte signaling mechanisms to differentially modulate CA1 input pathways. Male mice received viral injections at P35-P42, and acute hippocampal slices were prepared three weeks later for CA1 whole-cell electrophysiology or ex vivo two-photon astrocyte Ca^{2+} imaging. We recorded excitatory postsynaptic currents from CA1 pyramidal neurons while independently stimulating SR or SLM to evoke SC- or TA-mediated responses. Norepinephrine potentiated synaptic responses at both SC and TA synapses, indicating that adrenergic signaling enhances excitatory transmission across major CA1 inputs. However, activation of distinct adrenergic receptor families revealed pathway-specific modulation. The alpha1-adrenergic receptor agonist phenylephrine selectively enhanced SC-mediated responses, whereas the alpha2-adrenergic receptor agonist dexmedetomidine selectively enhanced TA-mediated responses. Astrocyte Gq manipulation further supports a role for astrocyte signaling in alpha1-adrenergic receptor-dependent potentiation of the SC pathway. To test whether these synaptic effects are associated with spatially distinct astrocyte activity, we imaged astrocyte Ca^{2+} dynamics in CA1 layers before and during adrenergic receptor activation. Preliminary imaging data suggest that norepinephrine, phenylephrine, and dexmedetomidine evoke layer-biased astrocyte Ca^{2+} responses across SR and SLM, consistent with receptor-specific recruitment of local astrocyte populations. Together, these findings support a model in which norepinephrine does not modulate CA1 through a uniform mechanism, but instead engages receptor- and layer-specific astrocyte signaling to regulate distinct hippocampal input

pathways. This work provides a framework for understanding how astrocyte heterogeneity contributes to pathway-specific neuromodulation and memory circuit function.

Disclosures: J. Kim: None. **C. Eroglu:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.03/N3

Topic: B.09. Glial Mechanisms

Support: Institute for Basic Science IBS-R001-D3 (B.-K.K.).

Title: Bifurcated astrocytic microdomain signaling confers engram specificity

Authors: *Y. JUNG[1,2], C.-H. KIM[2], H. PARK[4], B.-K. KAANG[3];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Sch. of Biol. Sci., [2]Inst. for Basic Sci., Daejeon, Korea, Republic of; [4]Inst. for basic science, Daejeon, Korea, Republic of

Abstract: <META NAME="author" CONTENT="정여진">AbstractLearning requires the selective strengthening of synapses within sparse engram networks, yet how this specificity is maintained across the broad astrocytic territory remains unclear1-5. Here, we show that astrocytes drive synapse-specific strengthening through bifurcated microdomain signaling during hippocampal engram maturation. By tracking the retrograde cascade initiated by intracellular growth hormone (GH) in the mouse dentate gyrus, we found that GH induces postsynaptic synthesis of endocannabinoid anandamide (AEA). The synthesized AEA acts as a dual-key signal that bifurcates into parallel astrocytic cascades: CB1 receptor activation drives the production of mature brain-derived neurotrophic factor (mBDNF), whereas TRPA1 channel activation induces localized extracellular Ca2+ influx that triggers its release. Neither pathway alone is sufficient to drive synaptic strengthening; instead, their coincidence within the astrocytic microdomain is required. Each pathway independently enforces a discrete layer of spatial restriction to prevent off-target paracrine spread. Disrupting either pathway abolishes synapse-specific plasticity and blocks engram maturation in vivo. These findings establish astrocytes as local biochemical integrators that implement microdomain-level coincidence detection to achieve synapse-specific plasticity within a shared territorial domain during memory formation.

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

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.04/N4

Topic: B.09. Glial Mechanisms

Support: JSPS KAKENHI grant 24K02128
JSPS KAKENHI grant 24KJ2074
JSPS KAKENHI grant JP22K15625
JST grant JPMJFR2249
AMED grant JP21km0908001
AMED grant JP22dk0207063
AMED grant P23jf0126004
AMED grant JP23wm0625001

Title: Memory reconsolidation by multiday astrocyte responses

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Abstract: Memories repeatedly undergo reactivation and reconstruction, thereby shifting between labile and stable states, the process called memory reconsolidation through which reactivated, destabilized memories are stabilized again and incorporated into a more enduring form of long-term storage. Previous studies have identified neuronal ensembles that become Fos-positive during experience and are reactivated during memory retrieval, termed engram cells. However, neuronal Fos alone, a plasticity marker that indicates circuit remodeling, is insufficient for memory restabilization, implying the need for additional cellular substrates. Here, we found a subset of astrocytes which is transcriptionally primed by an initial experience and then functionally triggered by repeated experiences for memory restabilization. Using our whole-brain Fos-dependent tagging and imaging method, we identified Fos-positive astrocyte populations (astrocyte ensembles) whose brain-wide distribution correlated with neuronal engrams and whose recruitment was broader during fear retrieval than during conditioning. Mechanistically, astrocyte Fos induction was dependent on a two-step state transition. First, the initial fear experience induced a slow, day-scale astrocytic state change with upregulation of noradrenaline receptor expression. Second, astrocytic responsiveness to noradrenaline was enhanced during fear retrieval. The integration of engram-derived and noradrenergic inputs induced a second astrocytic state transition characterized by Fos induction. Pharmacological and genetic interventions that disrupted signaling in these astrocyte ensembles impaired reconsolidation of reactivated memories. These findings suggest that astrocyte ensembles may constitute a multiday trace left by experience-dependent neural activity, acquiring eligibility to capture repeated experiences and thereby implementing memory reconsolidation at the level of a cellular ensemble. We further examined astrocyte ensembles in disease models in which memory reconsolidation is impaired, including Alzheimer's disease mouse models. To this end, we developed all-viral whole-brain Fos-tagging strategies that can be combined with transgenic mice. We will report altered brain-wide distribution of memory-relevant astrocyte ensembles in pathological states and the underlying cellular and circuit mechanisms.

Disclosures: K. Dewa: None. **K. Kaseda:** None. **J. Nagai:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.05/N5

Topic: B.09. Glial Mechanisms

Support: Innovation Technology Commission of the Hong Kong SARGrant 9445912
General Research Fund (GRF) of the Research Grants Council of Hong Kong (11103721, 11102820, and 11100018)

Title: mGluR5-Mediated Astrocytic Calcium Signaling Regulates EAAT2 Expression and Novel Object Recognition Memory

Authors: *Y. HUANG;
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Abstract: Astrocytic calcium signaling serves as an effector of neuronal activity via downstream metabolic pathways, but how these calcium signals are translated into metabolic support for memory formation remains poorly understood. Here, we identify metabotropic glutamate receptor 5 (mGluR5) in hippocampal astrocytes as a critical driver of calcium signals that link behaviorally-evoked glutamate release to excitatory amino acid transporter 2 (EAAT2) regulation and lactate production. Using fiber photometry, we show that mGluR5 is essential for both tonic and behaviorally evoked calcium activity in astrocytes. During novel object recognition (NOR), mGluR5-mediated calcium signaling responds to increased extracellular glutamate to promote EAAT2 membrane trafficking. This calcium pathway couples EAAT2 regulation to lactate production, linking glutamate signaling to metabolic support for cognitive processing. Disruption of this cascade, either through mGluR5 knockdown or calcium suppression, impairs lactate output and NOR performance, whereas restoration of calcium signaling via stromal interaction molecule 1 (STIM1) overexpression or chemogenetic Gq activation increase EAAT2 expression and metabolic function. These findings establish mGluR5-mediated astrocytic calcium signaling as a central hub that integrates glutamate sensing, EAAT2 regulation, and metabolic output to support hippocampal-dependent learning and memory.

Disclosures: Y. huang: None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.07/N7

Topic: B.09. Glial Mechanisms

Support: Research Grant from Vassar College
Internal Funding from Vassar College

Title: The role of glutamine synthetase in sustained attention in rats

Authors: *L. A. NEWMAN[1], **S. JACOBS**[1], R. RYAN MILLER[1], M. MARTINEZ[1], A. TAPIA[1], E. BAGADE[2], E. K. KHARITONOVA[1], W. XIE[1], D. D. KANGRIWALA[1], N. SILVERMAN-LLOYD[1], C. A. MENGDEN[1], J. BONANNO[1], D. RAI-GERSAPPE[1], A. D. CASCONE[1], S. ZHANG[1];
[1]Vassar Col., Poughkeepsie, NY; [2]Vassar Col., New York, NY

Abstract: Astrocytes recycle glutamate and GABA which can affect synaptic plasticity. One key component of this process is glutamine synthetase, which is found in the astrocytes and converts glutamate to glutamine which can then be transported back to neurons for further neurotransmission. While we, and other labs, have shown inhibiting glutamine synthetase with methionine sulfoximine can affect memory, the current experiments assess whether inhibition in the prelimbic cortex can affect sustained attention. Additionally, we examined if using ad libitum 2% citric acid (CA) water in the home cage as compared to water restriction to motivate behavior in operant chambers differentially affected glutamine synthetase inhibition as we previously saw CA can increase overall glutamine synthetase levels. Male and female Long Evans rats were trained on a sustained attention task requiring shaping to acquire the final task in which trials are presented at variable intervals (12 +/- 3 s) and rats must detect the presence of a light signal (25, 100, or 500 ms) by pressing one lever for a signal and another lever for a nonsignal. Rats received intracranial microinjections of methionine sulfoximine (0, 0.4, 2, or 10 mM in 0.5 µl saline, 0.25 µl/min) 15 min prior to testing. Vaginal smears were taken for female rats to assess whether performance changed based on estrogen levels at each estrous cycle phase. Inhibition of glutamine synthetase led to improvements in sustained attention performance, particularly in CA females, in a dose dependent manner. Our results suggest that glutamine synthetase in astrocytes is important for regulation of sustained attention in the prelimbic cortex.

Disclosures: L.A. Newman: None. **S. Jacobs:** None. **R. Ryan Miller:** None. **M. Martinez:** None. **A. Tapia:** None. **E. Bagade:** None. **E.K. Kharitonova:** None. **W. Xie:** None. **D.D. Kangriwala:** None. **N. Silverman-Lloyd:** None. **C.A. Mengden:** None. **J. Bonanno:** None. **D. Rai-Gersappe:** None. **A.D. Cascone:** None. **S. Zhang:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.08/N8

Topic: B.09. Glial Mechanisms

Support: NIMH-R01MH113743

Title: Perisynaptic astrocyte processes gate synapse vulnerability to microglia-mediated elimination

Authors: *Y.-H. LEE[1], T. E. FAUST[2], D. P. SCHAFER[3];
[1]Grad. Program in Neurosci., [2]Univ. of Massachusetts Chan Med. Sch., Worcester, MA;
[3]Neurobio., Univ. of Massachusetts Chan Med. Sch. Grad. Program in Neurosci., Upton, MA

Abstract: Neural circuit architecture is sculpted by the addition and selective removal of synapses. To maintain circuit stability while enabling adaptive remodeling, synapse removal must be tightly regulated and targeted to specific synapses. Microglia are now appreciated to engulf and remove synaptic material, but the upstream mechanism(s) dictating which synapses are removed by microglia remains an open question. Answers will offer new insight into how certain synapses are selected for removal in neural circuits during developmental synaptic pruning, adult plasticity, and diseases where synapse loss is an underlying core feature of pathogenesis. Microglia processes are highly dynamic, retracting and extending their processes to synapses continuously. Meanwhile, perisynaptic astrocytic processes (PAPs) maintain close, sustained contact with individual synapses, but they can adjust the degree of synaptic coverage or ensheathment based on neuronal activity and metabolic demands. Our recent findings demonstrated that these relatively stable PAPs can, in fact, remodel and move further away from synaptic membranes in response to microglia-derived Wnt signaling prior to synapse removal in the postnatal mouse cortex. Still, it remains unclear if PAP remodeling is necessary for downstream synapse removal by microglia. Here, we tested whether PAPs act as “gate keepers” of synapses such that the degree of PAP association with synaptic membranes dictates windows in which synapses are more vulnerable to removal by microglia. We first tested this concept in the rodent somatosensory cortex where astrocytes decrease their contact with synapses in advance of microglia-mediated synapse removal following removal of the whisker sensory input in neonate mice (postnatal day 4). We found that when the same whiskers removal procedure is performed in adult mice, astrocytes do not reduce contact with synapses and synapses are no longer removed by microglia. However, in mice with astrocyte-specific deletion of ezrin, a protein that form crosslinks between the actin cytoskeleton and plasma membrane in PAPs, whisker lesioning induced astrocyte retraction from synapses and synapse removal, suggesting that neonate-like plasticity can be reinstated in the adult somatosensory cortex by increasing PAP-synapse structural plasticity. We are further extending this concept into mouse models of neurodegeneration to determine if reduced PAP-synapse contact also increases synaptic vulnerability to removal by microglia during neurodegeneration.

Disclosures: Y. Lee: None. **T.E. Faust:** None. **D.P. Schafer:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.09/O1

Topic: B.09. Glial Mechanisms

Support: R01NS127819
R01NS113499
R01AG085666

Title: Complex and heterogeneous astrocyte electrical activity in response to neuronal activity

Authors: *M. ARMBRUSTER[1], J. GARCIA[1], C. G. DULLA[2];
[1]Tufts Univ., Boston, MA; [2]Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Astrocytes have traditionally been viewed as electrically passive cells in the CNS, with a hyperpolarized membrane potential that does not deviate significantly from their resting potential in response to physiological activity. Astrocytes are electrically coupled through gap junctions, have a very low membrane potential due to high K^+ conductance, which results in a very small membrane space constant. This space constant highlights that somatic patch clamp recordings are not sensitive to voltage changes in peripheral astrocytic processes (PAPs). Previously, we showed by using an astrocytic genetically encoded voltage indicator (GEVI), that PAPs in the somatosensory cortex have significantly larger and faster focal depolarizations. This challenged the view of largely invariant astrocytic membrane potential. Here using a next-generation GEVI (ASAP3) imaging of astrocytes in the somatosensory cortex, we show that astrocytes have multi-component repolarization kinetics, shaped by neuronal activity including the stimuli number and frequency. Additionally, using a novel correlation based image analysis algorithm, we show that PAPs have complex voltage responses including both depolarizations and hyperpolarizations. Many of the components that shape and contribute to these focal PAP voltage changes are not well understood. We have assayed mechanisms underlying the PAP voltage changes by using an adult focal astrocyte specific conditional knockout of Kir4.1, and 1μM Ouabain to inhibit the astrocyte specific α2 Na+/K+/ATPase. Here we started to establish the function of multiple elements that drive focal K+ changes following neuronal activity and can potentially shape downstream astrocytic and neuronal functions.

Disclosures: M. Armbruster: None. **J. Garcia:** None. **C.G. Dulla:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.10/O2

Topic: B.09. Glial Mechanisms

Support: Horizon 2020 ICT, DEEPER
Marie Skłodowska-Curie Fellowship, AdaM
Chan Zuckerberg Foundation

Title: Subcellular compartment-specific Ca^{2+} signaling in astrocytic cells during freely moving behavior

Authors: S. CURRELI[1], A. SATTIN[3], G. LETTI[2], L. MADDALENA[2], ***T. FELLIN**[2]; [1]Optical Approaches to Brain Function, [2]Inst. Italiano di Tecnologia, Genova, Italy; [3]Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: Astrocytes, the most abundant non-neuronal cell type in the mammalian brain, display complex changes in their intracellular calcium (Ca^{2+}), which can occur either in localized subcellular compartments (e.g., primary branches and perivascular endfeet) or propagate throughout the entire cell. In head-fixed mice, these astrocytic Ca^{2+} signals can be imaged using two-photon microscopy and have been shown to encode information about external sensory stimuli, task-related variables, and internal states. However, to date, two-photon imaging studies have been restricted to head-restrained preparations, thereby preventing the investigation of astrocytic Ca^{2+} signals in many forms of naturalistic and complex behavior. Here, we used miniaturized two-photon microscopes to image hippocampal astrocytes expressing the genetically encoded Ca^{2+} indicator GCaMP6f in mice engaging in freely moving spatial navigation in a two-dimensional arena. We observed two main classes of astrocytic Ca^{2+} signals: i) shorter-duration (lasting up to few seconds) spatially localized events, which were poorly correlated across astrocytic subcellular compartments; and ii) longer-duration (lasting up to tens of seconds) and spatially widespread events, which were highly correlated within individual astrocytes and across astrocytes. Both shorter- and longer-duration Ca^{2+} signals displayed distinct subcellular compartment-specific characteristics. Events in branches and perivascular endfeet exhibited larger amplitudes and higher frequency compared to those occurring in the astrocytic somata. Moreover, both Ca^{2+} signal classes displayed faster dynamics in branches compared to those in the cell somata, whereas Ca^{2+} signals in perivascular endfeet showed longer dynamics for longer-duration events compared to the same class of Ca^{2+} events occurring in the cell somata. Using a combination of multivariate regression analyses and machine-learning methods, we found that all astrocytic subcellular compartments encoded significant information about key behavioral variables, including animal position, navigation speed, and head direction. Together, these findings demonstrate that astrocytic Ca^{2+} dynamics display subcellular compartment-specific properties during freely moving spatial navigation and establish miniaturized two-photon imaging as a powerful approach to investigate the contribution of astrocytes to brain computation during naturalistic behavior.

Disclosures: S. Curreli: None. **A. Sattin:** None. **G. Letti:** None. **L. Maddalena:** None. **T. Fellin:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.11/O3

Topic: B.09. Glial Mechanisms

Title: Astrocyte-targeted Kalium channelrhodopsin activation modulates hippocampal CA1 neuronal activity in vivo

Authors: *Y. PAN[1,2], E. T. GILBERT[3], Z. PEI[3], C. M. BUHLER[3], D. F. ENGLISH[3], M. L. OLSEN[3];
[1]GBCB, [2]Genetics, Bioinformatics, and Computat. Biol., [3]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Astrocytes regulate hippocampal circuit excitability through membrane-potential-dependent control of extracellular ion homeostasis, neurotransmitter clearance, and neuron-glia signaling. However, whether acute modulation of astrocyte membrane potential is sufficient to alter CA1 neuronal activity *in vivo* remains unclear. Here, we used astrocyte-targeted Kalium channelrhodopsin, a naturally occurring K+-preferring light-gated channel, to perturb astrocyte membrane potential in mouse hippocampal CA1 *in vivo* and in acute hippocampal slices. We first characterized its cellular effect in astrocytes *in situ*. Whole-cell patch-clamp recordings from Kalium-expressing CA1 astrocytes showed light-evoked currents and a sustained mild depolarization. To determine whether this membrane-potential change was accompanied by local ionic effects, we used K+-sensitive microelectrodes in acute slices to monitor extracellular K+ ($[K^+]_o$) dynamics in CA1 during optical stimulation and found increased ($[K^+]_o$) during longer (500 ms) stimulations. Next, we combined *in vivo* optical activation of Kalium-expressing astrocytes with CA1 electrophysiological recordings to assess neuronal population responses. Short bursts of light activation (50 - 100 ms) of astrocytic Kalium altered CA1 neuronal excitability and oscillatory activity compared with baseline and control conditions. These effects were evaluated using local field potential activity, firing-rate measures, spectral power, and sharp-wave ripple-related events. Together, these experiments establish a workflow linking cellular validation of astrocyte membrane-potential modulation to circuit-level recordings *in vivo*. Our findings suggest that astrocyte membrane voltage is not a passive reflection of neuronal activity, but may act as an acute regulator of hippocampal network state. Astrocyte-targeted Kalium activation therefore provides a useful experimental strategy for testing causal relationships between astrocyte electrophysiology, extracellular ionic dynamics, and CA1 neuronal activity.

Disclosures: Y. Pan: None. **E.T. Gilbert:** None. **Z. Pei:** None. **C.M. Buhler:** None. **D.F. English:** None. **M.L. Olsen:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.12/O4

Topic: B.09. Glial Mechanisms

Support: NIH R01 NS129888
NIH R61 AG094651
Weill Neurohub

Title: Controlling endogenous calcium pathways in astrocytes using magnetogenetics

Authors: *T. TRAN[1], M. HERNANDEZ-MORALES[2], R. NATAN[3], N. JI[3], C. LIU[2];
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Abstract: Astrocytes exhibit complex spontaneous and evoked calcium dynamics which have been proposed to be responsible for many of their functions in the brain, including modulating neuronal circuitry. Modulating this calcium signaling in a manner resembling the complex dynamics observed under physiological conditions can help elucidate the roles of astrocytes in brain function. Here, we present pmFeRIC (plasma membrane Ferritin-iron Redistribution to Ion Channels), a magnetogenetic tool designed to control astrocyte calcium signaling by activating endogenous ion channels and calcium pathways. pmFeRIC consists of a plasma membrane-targeting motif (Lck) fused to a ferritin-binding linker (domain 5 of kininogen), which recruits endogenous ferritin to the cell membrane. Radiofrequency (RF) magnetic field stimulation induces ferritin-dependent reactive oxygen species (ROS) production, activating nearby ROS-sensitive endogenous ion channels. We show that RF stimulation evokes calcium responses in cultured hippocampal astrocytes and in visual cortex astrocytes of anesthetized mice. Astrocyte activation depends on RF-induced ROS generation leading to activation of native TRP channels and downstream calcium signaling pathways. RF-induced responses are dependent on the duration and amplitude of RF stimulation, and the calcium influx from ion channels at the membrane is amplified by calcium release from the endoplasmic reticulum. In the visual cortex, RF-induced responses in astrocytes expressing pmFeRIC closely resemble physiologically occurring calcium signals associated with locomotion. These findings demonstrate that endogenous calcium pathways in astrocytes can be selectively and remotely controlled, providing a powerful platform to investigate the causal roles of astrocyte calcium signaling in brain function.

Disclosures: T. Tran: None. **M. Hernandez-morales:** None. **R. Natan:** None. **N. Ji:** None. **C. Liu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.L. shares ownership of a patent application (WO2016004281 A1 PCT/US2015/038948) relating to the use of FeRIC for cell modulation and treatments.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.13/O5

Topic: B.09. Glial Mechanisms

Support: R01 NS120746

Title: Astrocytic-enriched TrkBT1 modulates acute behavioral and hippocampal network responses to subanesthetic Ketamine

Authors: *Z. PEI[1], C. M. BUHLER[3], Y. PAN[1], J. BROWNING[2], S. BASAK[6], S. JAHANBANI[4], K. SCHY[1], A. HUTCHINSON[5], D. F. ENGLISH[5], M. L. OLSEN[1]; [2]Neurosci., [1]Virginia Tech., Blacksburg, VA; [3]Sch. of Neurosci. : English Lab., [5]Neurosci., [4]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [6]Virginia tech, Blacksburg, VA

Abstract: The truncated TrkB.T1 receptor, an astrocyte-enriched isoform of the canonical receptor for brain-derived neurotrophic factor (BDNF), plays a critical role in astrocyte-neuron communication and glutamatergic synaptogenesis. Recent evidence suggests that fast-acting antidepressants, including ketamine, bind TrkB receptors, and because the full-length and truncated isoforms share complete extracellular and transmembrane sequence homology, TrkB.T1 may also contribute to ketamine's rapid effects. Here, we tested whether TrkB.T1 influences the behavioral and hippocampal network responses to a single subanesthetic ketamine injection. Adult wild-type (WT) and global TrkB.T1 knockout (KO) mice received saline or ketamine (30 mg/kg, i.p.) and were assessed in the elevated plus maze (EPM) or open field (OF) during the acute post-injection period. In parallel, CA1 local field potentials (LFPs) were recorded in awake head fixed animals with 1D locomotion Virtual Reality (VR) environments to evaluate ketamine-sensitive oscillatory dynamics. In WT mice, ketamine produced robust anxiolytic-like behavior, including increased open-arm exploration in the EPM, whereas this effect was not observed in TrkB.T1 KO mice. Preliminary LFP analyses indicate that subanesthetic ketamine alters CA1 theta activity and sharp wave ripple associated events in a genotype-dependent manner, suggesting that TrkB.T1 loss disrupts the maintenance of ketamine-responsive hippocampal network states. Together, these findings identify TrkB.T1 as a regulator of acute ketamine responses, linking astrocyte-enriched BDNF signaling to hippocampal circuit dynamics and anxiety-related behavior. Future work is aimed at completed these studies in astrocyte targeted, adult manipulation of TrkB.T1 to causally link astrocytes function to acute ketamine responses.

Disclosures: Z. Pei: None. **C.M. Buhler:** None. **Y. Pan:** None. **J. Browning:** None. **S. basak:** None. **S. Jahanbani:** None. **K. Schy:** None. **A. Hutchinson:** None. **D.F. English:** None. **M.L. Olsen:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.14/O6

Topic: B.09. Glial Mechanisms

Support: MST grant GTL24021-000
KIMST grant RS-2025-02292973

Title: Astrocytic Non-Canonical Ca^{2+} Signaling Induces a Catatonia Model Characterized by Waxy Flexibility

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Abstract: Catatonia is a severe neuropsychiatric syndrome characterized by profound motor abnormalities, including waxy flexibility. While traditional models focus on neuronal dysregulation within motor circuits, the role of astrocytic pathways remains unknown. In this study, we investigated how chlorpromazine affects astrocytic Ca^{2+} release and modulates synaptic transmission. We showed that chlorpromazine increased the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in the hippocampal CA1 region. In addition, this enhancement persisted even in the presence of tetrodotoxin (TTX), implicating an action potential-independent tripartite synaptic mechanism. Chlorpromazine induced a substantial elevation of astrocytic Ca^{2+} release. To identify the source of this massive Ca^{2+} release, we first confirmed via ER depletion that this Ca^{2+} does not originate from canonical ER Ca^{2+} stores. Organelle-specific Ca^{2+} imaging using nuclear, mitochondrial, and lysosomal markers subsequently demonstrated that lysosomes are the primary source of this Ca^{2+} release. Furthermore, the chlorpromazine-induced increase in sEPSC frequency was completely abolished by NPS2390, a group I mGluR1/5 antagonist. Astrocytic glutamate released via chlorpromazine-mediated non-canonical Ca^{2+} signaling increased presynaptic glutamate release through the activation of neuronal group I mGluR1/5. Sustained glutamatergic overdrive caused severe cytotoxicity in both neurons and astrocytes. Behaviorally, in the Open Field Test, chlorpromazine-treated mice exhibited characteristic sprawling immobility with all four limbs flaccidly extended. Taken together, our results show that chlorpromazine-induced astrocytic lysosomal Ca^{2+} elevation promotes synaptic hyperexcitability, establishing a catatonia model. This study provides the paradigm of catatonia pathophysiology toward an astrocyte-mediated mechanism.

Disclosures: H. Lim: None. **S. Lee:** None. **D. Woo:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.15/O7

Topic: B.09. Glial Mechanisms

Support: NIH R01 MH136275
BBRF (NARSAD) Young Investigator Grant

Title: Dopamine recruits striatal astrocytes to generate prolonged purinergic feedback and regulate behavioral engagement

Authors: *I. LAZARIDIS[1], G. AHN[1], E. A. HUESKE[1], K. HIROKANE[1], S. DRAMMIS[2], W. CHOI[3], A. M. GRAYBIEL[1];
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Abstract: Dopamine signaling in the dorsal striatum is essential for action selection, reinforcement learning, and behavioral flexibility, but how brief dopamine events are converted into longer-lasting changes in network and behavioral state remains unclear. Here, we identify a dorsal striatal astrocyte-dopamine-purine feedback loop that transforms phasic dopaminergic input into prolonged purinergic signaling and regulates task engagement. Using in vivo fiber photometry, optogenetics, dopamine and adenosine sensors, receptor-specific manipulations, and behavioral analyses in freely moving mice, we found that optogenetic activation of nigrostriatal dopamine neurons recruits dorsal striatal astrocytic Ca2+ responses through Drd2-dependent signaling. Brief dopamine events occurring over seconds were followed by slower extracellular adenosine signals lasting on the order of a minute, indicating that astrocytes can convert fast dopaminergic input into prolonged purinergic feedback. In the reverse direction, direct optogenetic activation of striatal astrocytes suppressed local dopamine release over a similar timescale, without producing detectable changes in spontaneous locomotion. During a self-initiated reinforcement-guided T-maze task, large striatal astrocytic Ca2+ transients preferentially marked transitions from disengagement to re-engagement, rather than immediate task events, reward outcomes, or aversive stimuli. Suppression of astrocytic Ca2+ signaling impaired task engagement and slowed learning, indicating that astrocyte activity is not only correlated with behavioral state transitions but contributes functionally to the ability of animals to enter and maintain an engaged state. Together, these findings define an in vivo dorsal striatal feedback architecture in which dopamine recruits astrocytes, astrocytes generate prolonged purinergic signaling, and astrocytic activation feeds back to regulate dopamine tone. We propose that this loop creates a transient reset window in which dopamine signaling is dampened, striatal output balance is shifted, and the circuit is positioned for transition into a new network and behavioral state.

Disclosures: I. Lazaridis: None. **G. Ahn:** None. **E.A. Hueske:** None. **K. Hirokane:** None. **S. Drammis:** None. **W. Choi:** None. **A.M. Graybiel:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.16/O8

Topic: B.09. Glial Mechanisms

Title: Astrocytic AMPARs Control NMDAR-mediated Synaptic Depression In The Striatum

Authors: *N. ELAZAR[1], J. R. RAVENEL[2], J. KIM[3], T. VAIDYANATHAN[4], M. R. TADROSS[5], C. EROGLU[6];

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Abstract: Astrocytes occupy a privileged position within neural circuits, extending processes that ensheath thousands of synapses and tile the brain with a broad sampling of the synaptic landscape. Astrocytes are active participants in synaptic function, responding to neuronal activity and influencing plasticity across brain regions. Yet a critical gap remains: how endogenous astrocytic receptor signaling contributes to synaptic function and circuit output in vivo is poorly understood, because existing approaches cannot selectively engage or inhibit native glial receptors with the cellular precision needed to distinguish their contributions from those of neurons sharing the same synaptic environment.This work addresses that gap directly. Using an astrocyte-targeted Drug Acutely Restricted by Tethering (DART) platform, we achieve cell-type-specific inhibition of endogenous astrocytic AMPA receptors (AMPARs) in the striatum with spatiotemporal precision. This approach allows us to ask, for the first time, what astrocytic glutamate sensing contributes to synaptic function in an intact circuit.We find that astrocytic AMPAR signaling is required to sustain excitatory drive onto striatal projection neurons. Acute receptor inhibition triggers a persistent suppression of excitatory transmission that mirrors long-term depression (LTD), dependent on ongoing synaptic activity and NMDA receptor engagement. Mechanistically, this plasticity is mediated through a non-ionotropic mode of NMDAR signaling and is linked to reduced astrocytic availability of D-serine — an endogenous NMDAR co-agonist — implicating glial transmitter release as a key effector. In vivo, unilateral astrocytic AMPAR blockade produces a slowly emerging turning bias without disrupting gross locomotion, consistent with a progressive, activity-dependent reorganization of striatal circuit function rather than acute transmission failure.Collectively, these findings reframe astrocytes as active participants in synaptic homeostasis: astrocytic glutamate sensing stabilizes excitatory strength through coordinated neuron-glia signaling, and its disruption is sufficient to reshape behavioral output. More broadly, this study establishes cell-type-specific acute pharmacology as a tractable strategy for dissecting glial contributions to neural computation — with implications for understanding circuit dysregulation in conditions where astrocyte function is compromised, including Parkinson's disease, addiction, and psychiatric disorders.

Disclosures: N. elazar: None. **J.R. Ravenel:** None. **J. Kim:** None. **T. Vaidyanathan:** None. **M.R. Tadross:** None. **C. Eroglu:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.17/P1

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01DA060724

Title: Astrocytic μ-opioid receptors modulate the acute effects of fentanyl on dopamine type 2 receptor-expressing striatal medium spiny neurons

Authors: *H. GOUDSWARD[1], V. YAROTSKYY[2], P. E. KNAPP[3], K. F. HAUSER[2], L. CONTOIS[4];
[2]Pharmacol. & Toxicology, [3]Dept Anat & Neurobio., [4]Pharmacol. and Toxicology, Sch. of Med., [1]Virginia Commonwealth Univ., Richmond, VA

Abstract: Opioid abuse and overdoses are one of the leading causes of death in the United States, with a large portion of these deaths involving the use of illicit fentanyl. Although μ-opioid receptor (MOR) expressing neurons mediate much of the abuse liability of opioids, activation of MORs in astroglia can modulate synaptic function and increase inflammatory cytokine release, which may contribute to the deleterious effects of fentanyl. Therefore, the goal of this study was to evaluate the role of astrocytic MORs in mediating the acute effects of fentanyl (100 nM) on dopamine type 2 receptor (D2) expressing medium spiny neurons (MSN) in the dorsolateral striatum. *Oprm1* was deleted in astrocytes using a Cre-loxP approach and *ex vivo* striatal slice electrophysiology recordings were performed. Our results showed that when MORs are deleted in astroglia, acute fentanyl application moderately increased action potential (AP) firing frequency in D2 MSNs at a 475-pA stimulus (p=0.0404, n=11), which was not observed in the control group. The resting membrane potential (p=0.178, n=11), the current causing half-maximum firing frequency (p=0.0973, n=11), and rheobase (p=0.1603, n=11) were not affected. The initial momentary frequency, a reciprocal to the duration of the first inter-action potential interval, and the latency to fire were also assessed. Fentanyl significantly increased the initial momentary frequency at stimuli between 400 and 525 pA, and reduced the first latency at stimuli above 350 pA in D2 MSNs from GFAP^{Oprm1}-Cre+ but not GFAP^{Oprm1}-Cre− mice. In addition, we demonstrated that fentanyl did not affect AP threshold but increased the AP half-width and decreased the AP amplitude and maximal AP upstroke velocity in both groups, which suggests a direct interaction with neuronal voltage-gated Na^+ and/or K^+ channels. Finally, to isolate whether the observed effects of fentanyl on D2 MSNs are due to intrinsic cellular effects or local synaptic changes, we applied fentanyl in the presence of antagonists for GABA-A (picrotoxin), NMDA (AP5), non-NMDA glutamate (CNQX), and glycine (strychnine) receptors. We found that in the presence of these antagonists, acute fentanyl application produced a significant (p=0.0013, n=10) decrease in evoked action potential firing at current steps greater than 175 pA. Overall, these results suggest that MOR-expressing astrocytes normally modulate the acute effects of fentanyl in the dorsolateral striatum by modifying neurotransmission and postsynaptic signaling through interactions with ionotropic glutamate, GABA, and/or glycine channels in D2 MSNs. Funding: NIH R01DA060724

Disclosures: H. Goudsward: None. **V. Yarotskyy:** None. **P.E. Knapp:** None. **K.F. Hauser:** None. **L. Contois:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.18/P2

Topic: B.09. Glial Mechanisms

Title: Astrocyte-mediated diffusion shapes action selection and learning in basal ganglia circuits

Authors: *C. I. CONNOLLY;
Computer Sci. Lab., SRI Intl., Menlo Park, CA

Abstract: Action selection in basal ganglia circuits is commonly modeled using channel-based competition frameworks such as the Gurney-Prescott-Redgrave (GPR) model, in which cortical salience signals are transformed into disinhibition of a selected motor program. While dopaminergic reward prediction error (RPE) signals are known to drive reinforcement learning within this architecture, the mechanisms underlying generalization and credit assignment across related actions remain unclear.
Here we propose that astrocyte networks provide a biophysical substrate for such generalization by implementing a diffusion process over action channels. We extend the GPR model by introducing an astrocyte state variable per channel that evolves according to a graph-based heat equation with local activity-dependent input and gap junction-mediated coupling. Astrocyte activity modulates effective salience and gates synaptic plasticity, yielding a diffusion-regularized form of temporal-difference learning. In this framework, astrocyte dynamics act as a probabilistic smoothing kernel over action space, distributing learning signals across neighboring channels.
Simulations demonstrate that dopamine-dependent learning alone produces highly local, rigid policies that fail to adapt when reward contingencies change. In contrast, the astrocyte-augmented model exhibits a transition from perseverative to flexible action selection as coupling strength increases. Incorporating successor representations and region-specific dopamine regimes further reveals that astrocytes enhance learning in intermediate regimes and stabilize behavior when phasic teaching signals are weak.
These results suggest that astrocyte syncytia impose a geometric structure on action space, enabling spatially extended credit assignment and stabilizing reinforcement learning in basal ganglia circuits.

Disclosures: C.I. Connolly: None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.19/P3

Topic: B.09. Glial Mechanisms

Title: Astrocyte-secreted Extracellular S100B Modulates Kv4.3 and CaV1.3 in Substantia Nigra Pars Compacta Dopaminergic Neurons of Mice

Authors: *S. RUFFINO[1], C. RODRIGUEZ[4], E. BANCROFT[2], R. SRINIVASAN[3];
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Abstract: Astrocytes express S100B, a calcium-binding protein that accumulates extracellularly in the midbrain and cerebrospinal fluid (CSF) of Parkinson's disease (PD) patients. In addition, human S100B polymorphisms that increase S100B secretion are associated with increased risk for PD in humans. Furthermore, preclinical studies show that S100B overexpression in mice produces PD-like features, while S100B ablation protects against neurotoxin-induced dopaminergic (DA) neuron loss. In the context of these compelling data, we previously used DA neuron-astrocyte co-cultures to demonstrate that acute exposure to 50 pM of bath-applied S100B peptide selectively inhibits A-type voltage gated potassium (Kv4.3) currents and enhances L-type calcium influx specifically in DA neurons. These data suggested that extracellularly secreted S100B by astrocytes may drive early DA dysfunction in PD through coordinated actions on Kv4.3 and L-type voltage gated calcium channels (L-type VGCCs). Therefore, in this study, we sought to examine the specific role of secreted S100B from midbrain astrocytes on SNc DA neuron pathophysiology. To do this, we first developed two astrocyte-specific AAVs: secretable-S100B (sec-S100B) expressing full-length S100B, and non-secretable-S100B (non-sec-S100B), generated by a single amino-acid deletion in the C-terminal ERES motif. Primary midbrain DA neuron-astrocyte co-cultures were exposed to sec- or non-sec-S100B for five days and co-immunostained for tyrosine hydroxylase (TH) and Kv4.3. We found that when compared to non-sec-S100B, sec-S100B expression in midbrain cultured astrocytes differentially altered Kv4.3 in expression in DA somata and processes, demonstrating that sec-S100B mediates compartment-specific Kv4.3 remodeling in DA neurons. In parallel, we performed GCaMP6f imaging following acute application of 10 micromolar of the L-type VGCC blocker, nifedipine to midbrain astrocyte-DA neuron co-cultures. These experiments demonstrated differential effects on calcium fluxes in DA neurons between sec- and non-sec-S100B. We next tested the chronic effects of S100B secretion by SNc astrocytes in vivo, by injecting sec- or non-sec-S100B into the SNc of male and female mice. We found that sec-S100B significantly increased Kv4.3 intensity in DA somata and processes, suggesting compensatory Kv4.3 upregulation following initial inhibition by secreted S100B in vivo. Together, these data support a model in which astrocyte-secreted S100B modulates Kv4.3 and CaV1.3 function in SNc DA neurons, driving calcium dysregulation and DA neuron vulnerability that underlies early PD pathophysiology.

Disclosures: S. Ruffino: None. **C. Rodriguez:** None. **E. Bancroft:** None. **R. Srinivasan:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.20/P4

Topic: B.09. Glial Mechanisms

Support: R01NS124037

Title: CD38 deficiency alters gliovascular homeostasis in the substantia nigra through astrocyte endfoot-associated molecular changes

Authors: ***S. BASAK**[1], R. M. COWELL[2], M. L. OLSEN[3];
[1]Virginia tech, Blacksburg, VA; [2]Neurol., Univ. Alabama at Birmingham, Birmingham, AL;
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Abstract: CD38 is a multifunctional ectoenzyme that regulates NAD^+ metabolism and cellular bioenergetics, and genetic variation in CD38 has been linked to Parkinson's disease (PD). However, its role in astrocyte biology and gliovascular function remains poorly understood. Here, we investigated the impact of CD38 deficiency on astrocyte-endfoot organization in the murine midbrain and substantia nigra (SN). RNA sequencing of isolated astrocytes revealed broad transcriptional alterations involving mitochondrial function, cellular metabolism, senescence, astrocyte reactivity, and pathways associated with PD and Alzheimer's disease. Given the enrichment of end-foot-associated pathways in CD38-deficient astrocytes, we investigated astrocyte-endfoot and gliovascular organization in SN. By cross-referencing our midbrain RNA-seq dataset with published astrocyte endfoot signatures, we identified 113 and 211 dysregulated endfoot-associated genes in *Cd38*$^{+/-}$ and *Cd38*$^{-/-}$ mice, respectively. Subsequent immunohistochemical analyses demonstrated reduced AQP4 expression in the substantia nigra pars compacta (SNc). Imaris filament tracing revealed vascular remodeling in CD38-deficient mice, characterized by reduced vessel diameter, length, and volume, accompanied by increased branching angles. Microvessel-endfeet proteomics revealed disruptions in transport, gliogenesis, protein localization, cell adhesion, and mitochondrial proton-motive force, supporting a role for CD38 in maintaining astrocyte-endfoot and gliovascular homeostasis. Together, these findings identify a previously unrecognized role for Cd38 in maintaining astrocyte-endfoot organization and gliovascular homeostasis, suggesting that astrocytic dysfunction may contribute to selective neuronal vulnerability via altering the gliovascular network.

Disclosures: S. basak: None. **R.M. Cowell:** None. **M.L. Olsen:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.21/P5

Topic: B.09. Glial Mechanisms

Support: DoD Grant W911NF2410047

Title: Astrocytes Sense and Respond to Neuronal Acute Insulin Resistance

Authors: ***A. ROSZCZYK**[1], E. BALBUENA[1], S. CHITTARANJAN[2], T. BUBEL[3], N. A. SMITH[4];

[1]Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [2]Univ. of Rochester Neurosci. Grad. Program, Rochester, NY; [3]Univ. of Rochester, Rochester, NY; [4]Dept. of Neurosci., Univ. of Rochester, Webster, NY

Abstract: Title Astrocytes Sense and Respond To Neuronal Acute Insulin Resistance
AuthorsA. Roszczyk, E. Balbuena, S. Chittaranjan, T. Bubel, N.A. Smith
Abstract
Type 2 Diabetes (T2D) has emerged as a rapidly growing disease. Though commonly characterized in peripheral organs, T2D also affects brain function. Insulin resistance (IR), a defining trait of T2D, impairs insulin signaling and thereby disrupts the surface expression of the glucose transporter GLUT4. Insulin-sensitive neuronal subsets in regions such as the hippocampus express GLUT4. Thus, during IR, neurons in these regions have reduced glucose uptake and become hypometabolic. In this context, astrocytes play a key role in preserving proper neuronal function and energetics, though the immediate changes they undergo during this neuronal stress are poorly understood. Many of their functions, such as the release of neuromodulators and potassium buffering, are calcium dependent. Astrocytes also respond to neurotransmitters via calcium signaling, making calcium a key integrative signal in these cells. This project seeks to understand how astrocyte integration of neuronal stress via calcium signaling changes in a model of neuronal acute insulin resistance (AIR).
To induce AIR, we pharmacologically inhibited GLUT4 with indinavir in acute brain slices. Using 2-photon microscopy, we then imaged calcium dynamics in hippocampal astrocytes from Aldh1l1-CreERT2 x LSL-GCaMP5g/tdTomato mice (male and female, P56 - P90) in either control or AIR conditions. During AIR, the frequency of both somatic and process events increased (somas: $p < 0.0001$; processes: $p < 0.0001$), as did the average peak of somatic events ($p < 0.0001$). Additionally, there were no significant differences in calcium dynamics between sexes, although the average somatic event peak for males trended higher than for females ($p = 0.0589$). All statistics were done using a 2-Way ANOVA with Tukey's post-hoc; N = 6 mice (3 males, 3 females). These results indicate that during AIR, astrocytes undergo changes in their calcium dynamics and are acutely tuned into neuronal hypometabolism. Future experiments will examine this effect across the lifespan as the brain's functional and metabolic flexibility diminishes. We will also use metabolic assays in culture to understand how the energetics of both neurons and astrocytes change during AIR. These experiments will provide insight into how astrocytes maintain homeostasis on an acute timescale and may identify functions that are lost or reduced during aging, thereby rendering the brain more susceptible to metabolic stress.

Disclosures: A. Roszczyk: None. **E. Balbuena:** None. **S. Chittaranjan:** None. **T. Bubel:** None. **N.A. Smith:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.22/P6

Topic: B.09. Glial Mechanisms

Support: Institute for Basic Science (IBS), Center for Memory and Glioscience (IBS-R001-D2 to C.J.L.)

Title: Corticosterone increases MAOB-dependent H_2O_2 production in astrocytes.

Authors: *J. JOO[1], J. KIM[2], C. LEE[3];
[1]Ctr. for Memory and Glioscience, Inst. for Basic Sci. (IBS), Univ. of Sci. and Technol. (UST), Daejeon, Korea, Republic of; [2]Ctr. For Cognition and Sociality/Ibs, Daejeon, Korea, Republic of; [3]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Astrocytic hydrogen peroxide (H_2O_2) has traditionally been viewed as a pathological consequence of reactive astrogliosis, particularly under neuroinflammatory or neurodegenerative conditions. However, emerging evidence suggests that transient, spatially restricted H_2O_2 can also act as a redox signaling molecule, modulating neuron-glia communication. Here, we investigated whether corticosterone (CORT), a major stress hormone in rodents, induces astrocytic H_2O_2 production as a regulated redox signal that may be involved in stress-associated memory processes. RNA-seq analysis revealed significant upregulation of polyamine metabolism-related genes, including antizyme inhibitor (AZIN1) and Spermidine/Spermine N1-Acetyltransferase 1 (SAT1). Using newly developed genetically encoded H_2O_2 sensors, oROS-g and oROS-g1R, in primary astrocytes, we found that 10 μM or 100 μM of CORT robustly increased H_2O_2 signals. Pharmacological dissection demonstrated that the glucocorticoid receptor antagonist RU486 strongly attenuated the CORT-evoked H_2O_2 response by 92.1%, the MAO-B inhibitor KDS2010 by 75.14%, the ODC1 inhibitor 15010 by 38.9%, combined KDS2010 and 15010 treatment by 82.1%, and the MEK inhibitor PD98059 by 69.1%. These results suggest that CORT-induced astrocytic H_2O_2 generation is mediated through glucocorticoid receptor-dependent signaling and involves MAO-B-, ODC1-, and MEK-associated pathways. In C57BL/6 mice, intraperitoneal injection of CORT at 1 mg/kg increased H_2O_2 levels as measured by the ROS-Glo assay, with a rapid elevation observed 5 minutes after injection and a return to vehicle-comparable levels by 30 minutes. Direct enzyme inhibition assays further showed that CORT did not directly inhibit MAO-B or ODC1, supporting the idea that CORT regulates H_2O_2 production through upstream signaling rather than direct enzymatic inhibition. Finally, in vivo fiber photometry of hippocampal CA1 oROS-g1R expression revealed a CORT-responsive H_2O_2 signal 30 min after intraperitoneal injection of 10 mg/kg CORT. Together, these findings identify CORT-evoked astrocytic H_2O_2 as a rapid and regulated redox signal rather than merely a marker of oxidative damage. These results provide a potential basis for future studies on how stress-induced astrocytic H_2O_2 signaling may influence astrocyte-neuron communication, neuronal protection, and memory formation.

Disclosures: J. Joo: None. **J. Kim:** None. **C. Lee:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.23/Q1

Topic: B.09. Glial Mechanisms

Support: NIH R21 NS140782

Title: LRRC8D-Containing Volume-Regulated Anion Channels Dominate Swelling-Activated Taurine Release in the Brain but Are Dispensable for Systemic Osmoregulation

Authors: *M. L. CHANDLER, J. W. NALWALK, P. DOHARE, A. SPRAGUE, A. A. MONGIN;
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Abstract: Volume-regulated anion channels (VRACs) are swelling-activated Cl^- channels formed by heteromers of LRRC8 proteins (LRRC8A-E). VRACs are activated by cell swelling and mediate regulatory volume decrease (RVD) by releasing Cl^- and organic osmolytes, including amino acids such as taurine. In the brain, taurine functions as both an osmolyte and an inhibitory neuromodulator, acting as an agonist of glycine and $GABA_A$-receptors. In the hypothalamus, decreases in interstitial osmolarity are thought to stimulate the release of astrocyte-derived taurine, which inhibits magnocellular neurons and suppresses pituitary secretion of the antidiuretic hormone arginine vasopressin. Here, we used RNAi and genetically modified mice to (i) determine the contribution of LRRC8 subunits to swelling-activated taurine release, and (ii) investigate the role of brain VRACs in whole-body osmoregulation. The contribution of VRACs to swelling-activated taurine release was assessed both *in vitro* and *in vivo* using a brain-wide knockout of the essential VRAC subunit LRRC8A (bLRRC8A KO, $Nestin^{Cre}$-driven excision of floxed *Lrrc8a*). In LRRC8A-null astrocyte cultures, swelling-activated release of radiolabeled [^{3}H]taurine was reduced by ≥80% compared to controls. Consistent with these findings, *in vivo* microdialysis revealed a 76% reduction in swelling-activated taurine release in bLRRC8A KO brains relative to littermate controls. Together, these results demonstrate that LRRC8A-containing VRACs constitute a primary pathway for swelling-induced taurine release in the brain. We next used RNAi and radiotracer assays to assess the functional contributions of the complementary LRRC8B-E subunits and confirmed LRRC8D as a key determinant of VRAC-mediated taurine release. RNA-seq analysis further showed that *Lrrc8d* is enriched in the hypothalamus, where taurine is thought to modulate fluid-electrolyte homeostasis. To test whether brain VRACs contribute to systemic osmoregulation, we measured recovery from hypoosmotic challenge in two animal models: the bLRRC8A KO and a gene trap-mediated LRRC8D depletion model. Genetically modified and control mice were challenged with an intraperitoneal injection of sterile water (7.5% body weight, under anesthesia), and serum osmolarity was monitored over time. Contrary to our hypothesis, neither VRAC-deficient model showed a delay in recovery from hypoosmotic challenge. Overall, this study identifies LRRC8A/D-containing VRACs as the primary conduit for swelling-activated taurine release in the brain, yet indicates that this pathway is not essential for systemic fluid-electrolyte homeostasis.

Disclosures: M.L. Chandler: None. **J.W. Nalwalk:** None. **P. Dohare:** None. **A. Sprague:** None. **A.A. Mongin:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.24/Q2

Topic: B.09. Glial Mechanisms

Support: NIH R35 NS122172
the Howard Hughes Medical Institute

Title: A neuron-glia circuit anticipates hypoxia to regulate organismal oxygen use

Authors: *Z. WEI[1], R. ZHANG[2], J. HOW[3], M. NARDIN[2], S. NARAYAN[5], A. KINKHABWALA[6], W. CHEN[7], J.-X. LIM[2], V. RUETTEN[2], M. HAESEMEYER[8], B. MENSH[4], M. C. FISHMAN[9], F. ENGERT[10], B. BABADI[11], J. DU[12], D. PROBER[13], M. B. AHRENS[14];
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Abstract: Organisms must regulate metabolic resources such as oxygen (O_2) and nutrients despite environmental variability and the energetic costs of their own actions. Such regulation can occur reactively, through homeostatic corrections of recent imbalances, or predictively, through allostatic adjustments that anticipate future demand. Predictive regulation is particularly important because metabolic resources often continue to be consumed for seconds to minutes after motor actions cease as tissues repay incurred costs, making it advantageous to prevent depletion before it occurs. However, the cellular and circuit mechanisms for allostatic control remain largely unknown. Using whole-brain neuronal and astroglial imaging and O_2 measurements in behaving zebrafish, we identified a noradrenergic-astroglial circuit that detects, anticipates, and prevents internal O_2 depletion. We found that swimming exacerbated internal hypoxia with a multi-second delay, but behavioral adaptations occurred before such self-generated hypoxia manifested, suggesting predictive control, confirmed using computational modeling. Noradrenergic neurons in the nucleus of the solitary tract directly detected brain hypoxia and received efference copies of swimming actions; these inputs summed at the level of membrane voltage to increase spiking and norepinephrine release when actions and resource scarcity co-occurred. Astroglia integrated noradrenergic input into prolonged Ca^{2+} elevation that tracked the O_2 cost of recent actions and thereby predicted O_2 debt relative to O_2 availability, rising ~8 s before O_2 fell. This astroglial prediction reorganized brain-wide activity to suppress locomotion and promote respiration, preempting O_2 depletion. Silencing noradrenergic neurons or astroglial signaling abolished these hypoxia coping behaviors, whereas selective activation evoked them. This neuronal-astroglial mechanism constitutes a predictive control system that integrates physiological state with behavioral intent to avert metabolic crisis, revealing a cellular substrate for proactive energy management.

Disclosures: Z. Wei: None. **R. Zhang:** None. **J. How:** None. **M. Nardin:** None. **S. Narayan:** None. **A. Kinkhabwala:** None. **W. Chen:** None. **J. Lim:** None. **V. Ruetten:** None. **M. Haesemeyer:** None. **B. Mensh:** None. **M.C. Fishman:** None. **F. Engert:** None. **B. Babadi:** None. **J. Du:** None. **D. Prober:** None. **M.B. Ahrens:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.25/Q3

Topic: B.09. Glial Mechanisms

Support: GRF Grant 14114324

Title: An ER localized kinase VRK2 is highly expressed in perivascular glia

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Abstract: Vaccinia-Related Kinase 2 (VRK2) is a serine-threonine kinase repeatedly identified by large-scale genome-wide association studies as a risk gene for multiple neuropsychiatric disorders, including schizophrenia, major depressive disorder, and epilepsy. Despite these strong genetic associations, the mechanisms by which VRK2 is involved in neuropathology remain largely unknown. Here, we generated a custom antibody against VRK2 and mapped its expression across postnatal mouse brain regions. We found that VRK2 is robustly expressed in hippocampus, cortex, and corpus callosum. Co-staining with cell type-specific markers further revealed that VRK2 expression in both microglia and astrocytes, with notable enrichment in perivascular region. In cultured human astrocytes, VRK2 localized to the endoplasmic reticulum (ER) membrane and was distributed from the soma to distal cellular processes. These findings identify perivascular glia as a prominent cellular site of VRK2 expression and suggest that VRK2 may play a role in maintaining brain homeostasis through glial cells.

Disclosures: S. Yang: None. **B. Gao:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.26/Q4

Topic: B.09. Glial Mechanisms

Support: NIH BRAIN Initiative U19 Research Program (1U19NS128613-01, HiH, MN)
Novo Nordisk Foundation (NNFOC0058058, HiH)
Danmarks Frie Forskningsfond (0134-00107B, HiH)
JSPS KAKENHI (22K06454/24H01221, AK; 24K18240, TY;
JP23H02782/JP24H00861, MS)
JST ACT-X (JPMJAX211K, TY)
AMED Brain/MINDS (JP21dm0207111, HiH)
AMED Brain/MINDS 2.0 (JP24wm0625103, HiH; JP24wm0625119, MS)
the Lundbeck Foundation (R360-2021-613, R436-2023-1219)
Ono pharmaceutical (HiH)
Marie Skłodowska-Curie Fellowship ANCoDy (101064009, AA)
ONO Rising Star Fellowship (AA)

Title: Cerebral blood flow is modulated by astrocytic cAMP elevation independently of IP_3R2-mediated Ca^{2+} signaling in mice

Authors: *M. VITTANI[1], R. HERLO[2], X. WANG[3], T. MISHIMA[2], P. KUSK[2], A. KONNO[4], H. HIRAI[5], T. TSUBOI[6], T. KITAGUCHI[7], C. KJAERBY[2], A. ASIMINAS[2], T. YOKOYAMA[8], M. SAKAMOTO[8], M. NEDERGAARD[9], H. HIRASE[2];
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Abstract: During functional hyperemia, local neural activity increases cerebral blood flow (CBF). Astrocytes are well positioned to regulate CBF because they enwrap cerebral blood vessels and respond to neuronal activity through G protein-coupled receptor signaling via the second messengers calcium (Ca^{2+}) and cyclic adenosine monophosphate (cAMP). Whereas Ca^{2+} signaling has been widely studied in neurovascular coupling, the role of astrocytic cAMP remains less clear. We tested whether astrocytic cAMP elevation is sufficient to modulate CBF. Adeno-associated viral vectors were engineered to express a bacterial photoactivated adenylyl cyclase selectively in astrocytes, allowing blue light-evoked cAMP elevation. Optogenetic stimulation also induced astrocytic Ca^{2+} elevations, although Ca^{2+} responses appeared with a delayed onset under mild stimulation conditions. *In vivo* imaging through a thinned skull in anesthetized and awake mice showed that astrocytic cAMP elevation induced robust arteriole dilation. In awake mice, dilation began after ~1.8 s and reached its maximum within 10 s, whereas responses were slower under anesthesia. Mild stimulation, producing sensory-level cAMP elevations, was sufficient to evoke vasodilation. This response persisted in IP_3 receptor type 2 knockout mice, indicating that astrocyte-cAMP-induced vasodilation does not require GPCR-induced intracellular Ca^{2+} release. These results identify astrocytic cAMP as a key modulator of cerebral vasodilation and local CBF regulation. This mechanism may be relevant to neurological conditions involving impaired blood flow regulation.

Disclosures: M. Vittani: None. **R. Herlo:** None. **X. Wang:** None. **T. Mishima:** None. **P. Kusk:** None. **A. Konno:** None. **H. Hirai:** None. **T. Tsuboi:** None. **T. Kitaguchi:** None. **C. Kjaerby:** None. **A. Asiminas:** None. **T. Yokoyama:** None. **M. Sakamoto:** None. **M. Nedergaard:** None. **H. Hirase:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.27/Q5

Topic: B.09. Glial Mechanisms

Title: Modulating astrocyte endfeet to increase blood-brain-barrier permeability

Authors: *H. NI[1], R. H. FRIEDEL[2], H. ZOU[3];
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Abstract: The blood-brain-barrier (BBB) protects the neural microenvironment but simultaneously poses a major hurdle for drug delivery to the central nervous system (CNS). Existing BBB opening strategies primarily target endothelial cells, leaving astrocyte endfeet that ensheath brain microvasculature largely unexplored from a therapeutic standpoint. Here, we show that astrocyte endfeet polarization and anchorage require guidance receptor Plexin-B1. Constitutive or astrocyte-specific Plexin-B1 deletion disrupted mitochondrial congregation, endosomal trafficking, and membrane stability at endfeet, leading to reduced aquaporin-4 and collagen IV. These changes enhanced BBB permeability, enabling passage of high-molecular-mass tracers and enhanced delivery of intravenously administered adeno-associated virus (AAV) into the brain parenchyma. Ultrastructural analysis revealed swollen astrocyte endfeet, increased endothelial vesicular trafficking, a hallmark of enhanced transcytosis, but intact tight junctions in Plexin-B1 KO mice. Single-cell transcriptomics linked Plexin-B1 to astrocyte polarity and mitochondrial function, while lipidomic profiles revealed altered lipid environment. Collectively, our study identifies Plexin-B1 as a critical regulator of astrocyte endfoot integrity and demonstrates that targeting astrocyte endfeet represents a viable strategy for size-selective BBB opening to enhance CNS drug delivery.

Disclosures: H. Ni: None. **R.H. Friedel:** None. **H. Zou:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.28/Q6

Topic: B.09. Glial Mechanisms

Title: Disrupting Astrocytic Endfeet Mitochondrial Calcium Signals Via Novel AAV Mito-Ncs1 Within The Dorsolateral Striatum Of Mice Alters The Blood-Brain Barrier

Authors: *G. HALL[1], D. AYALA[4], L. F. LOPEZ VILLAGRAN[2], Z. KHAN[6], A. PAULSON[1], S. BAKE[5], R. SRINIVASAN[3];
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Abstract: Astrocyte calcium signals have emerged as a primary mechanism of communication with neurons. While it is known that astrocytes are coupled to the blood-brain barrier (BBB) via endfoot processes, the relationship between astrocytic endfoot calcium signals and the BBB is not well understood. In this study, we assessed the role of astrocytic mitochondrial calcium events in maintaining BBB integrity. To do so, we altered calcium flux events in astrocytic mitochondria within the dorsolateral striatum (DLS) of male and female C57Bl6J mice with a novel AAV, called Mito-NCS1. This AAV expresses the neuronal calcium buffer, NCS1, only in astrocytic mitochondria. Another AAV, Mito-GCaMP6f was used to visualize calcium events in astrocytic mitochondria. Both AAVs were stereotaxically co-injected in the DLS and calcium flux events were characterized using AQUA2 software. We found changes in non-propagating calcium events in astrocytes expressing Mito-NCS1, namely a decrease in frequency and an increase in event area size. We next examined Mito-NCS1-induced changes in mitochondrial morphology by co-injecting DLS astrocytes with Mito-NCS1 and an AAV specifically expressing GFP in the astrocytic mitochondria of the DLS, called Mito-GFP, using MitoGraph software. We found an overall decrease in mitochondrial connectivity, with a paradoxical increase in mitochondrial connectivity in the end feet. This led us to assess expression of the astrocyte endfoot protein, Aqp4, astrocyte reactivity with GFAP, and microglial reactivity with Iba-1. We found a significant decrease in the expression of Aqp4, an increase in GFAP, and no changes in Iba-1. Finally, using WGA vessel labeling, DISCO tissue clearing, and 3D light-sheet microscopy, we assessed functional changes to the BBB. Together, these results suggest that calcium signals in astrocytic mitochondria within the DLS play a critical role in BBB biology.

Disclosures: G. Hall: None. **D. Ayala:** None. **L.F. Lopez Villagran:** None. **Z. Khan:** None. **A. Paulson:** None. **S. Bake:** None. **R. Srinivasan:** None.

Poster

PSTR216: Astrocytes: Signaling, Synaptic Regulation, and Circuit Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR216.29/R1

Topic: B.09. Glial Mechanisms

Support: University of Pittsburgh Department of Neurology Start-up funding (GB)

Title: Astrocytic NBCe1 Deletion Prevents Depolarization of Perivascular AQP4 and α-Syntrophin Localization in Ischemic Stroke

Authors: *G. GAO[1,2], U. WARRAICH[1], E. BERTHOLD[1], O. CAPUK[1], V. FIESLER[1,3], Y. YIN[2], G. BEGUM[1,3];
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Abstract: Perivascular astrocytic endfeet are specialized membrane domains enriched in channels, transporters, receptors and enzymes critical for astrocyte-vascular interactions. Disruption of endfoot organization, including the loss of polarized expression of key proteins such as aquaporin-4 (AQP4), contributes to vascular dysfunction and edema formation following ischemic stroke, yet the underlying mechanisms remain poorly understood. Here, we investigated the role of astrocytic electrogenic sodium bicarbonate transporter 1 (NBCe1/SLC4A4), preferentially polarized to astrocytic endfeet, in ischemic stroke and its impact on the perivascular endfeet damage. NBCe1 plays important role in brain pH homeostasis, but its functional role in these specialized membrane domains remains unclear. We used tamoxifen inducible *Gfap-Cre$^{ERT2+/-}$;Nbce1$^{f/f}$* mice to selectively delete *Nbce1* in GFAP^{+} reactive astrocytes. In wild-type (WT) mice 3 days after middle cerebral artery occlusion (MCAO) induced stroke, immunocytochemistry revealed AQP4 depolarization characterized by loss of perivascular expression and increased parenchymal distribution. This was accompanied by disrupted expression of the scaffold protein α-syntrophin, which anchors AQP4 to the endfeet. In contrast, *Nbce1* cKO mice showed reduced AQP4 puncta within reactive astrocytic somata and a higher perivascular AQP4 polarization ratio in ischemic regions, along with preserved perivascular α-syntrophin expression. To further investigate potential interactions among these proteins, immortalized human astrocytes (hTERT) were subjected to in vitro ischemia using 3 h of oxygen-glucose deprivation (OGD) followed by reoxygenation (REOX). Increased expression of NBCe1, AQP4, and α-syntrophin were detected and co-association of NBCe1 with AQP4 was confirmed by immunoprecipitation of AQP4 followed by Western blot analysis for NBCe1 protein, suggesting their enhanced interaction under ischemic conditions. Together, these findings suggest that ischemic stroke disrupts perivascular AQP4 polarization, potentially through alterations in NBCe1 protein. Whether preservation of α-syntrophin localization in *Nbce1* cKO stroke brains contributes to this effect remains to be determined. Collectively, these results support a role for astrocytic NBCe1 in regulating endfoot organization following ischemic stroke.

Disclosures: G. Gao: None. **U. Warraich:** None. **E. Berthold:** None. **O. Capuk:** None. **V. Fiesler:** None. **Y. Yin:** None. **G. Begum:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.01/R2

Topic: B.10. Neuro-Oncology

Support: CA269365

Title: Neutrophils give up mitochondria to cancer cells supporting GBM progression.

Authors: *N. FILIPPOVA[1], J. SHI[1], X. YANG[2], C. SOROCHINSKY[3], L. B. NABORS[2]; [2]Neurol., [1]UAB, Birmingham, AL; [3]Harvard Col., Cambridge, MA

Abstract: Background: Mitochondria-directed tissue reprogramming is increasingly recognized as playing a significant role in many diseases, including gliomas. Current knowledge of mitochondria-directed tissue reprogramming in gliomas is based on the investigation of brain-resident cells without accounting for the unique population of myeloid-derived cells, specifically neutrophils, which arise from skull bone marrow, undergo significant expansion, and intracranial infiltration. **Methods:** We investigated intercellular mitochondrial transfer from neutrophils to glioma cells using both *in vitro* and *in vivo* approaches. GBM mouse models with EGFP-tagged neutrophil mitochondria and RFP-expressing tumors were used to track mito-transfer. To investigate mito-transfer *in vitro*, we co-cultured PDGx cells expressing EGFP and a neutrophil-like differentiated HL60 cell lines containing mitochondria labelled with mito-probe or mito-DsRed fluorescence protein fused with mito-targeting sequence from subunit VIII of human cytochrome C oxidase. A genome-wide CRISPR knockout screening in PDGx cells and an RNA-seq approach were employed to identify genes and pathways involved in neutrophil-guided mito-transfer. The functional consequences of mito-acquisition were assessed through analysis of tumor cell proliferation, ROS, and mitoDNA production *in vitro,* and mouse survival *in vivo.* **Results:** Neutrophils were identified as a source of mito-transfer to glioma cells both *in vitro* and *in vivo*. The non-mito-recipient population isolated from genome-wide screening was less aggressive*,* with overall mouse survival twice as long as mice bearing mito-recipient tumors. Gene enrichment and validation analyses revealed perturbations of lncRNA and genes responsible for mitochondrial subcellular distribution, fusion/fission dynamics, and CD81-dependent TNT formation in non-recipient PDGx cells. RNA-seq data revealed a significant decline in the EMT transition, as well as in the TNF-alpha (via NF-kB) and TNF-beta cell signaling pathways, IL-6/JAK/STAT3, and inflammatory responses. Mitochondria were purified from primary mouse neutrophils and applied to tumor cells to assess the direct power of neutrophil mitochondria on proliferation capacity, ROS, and mitoDNA content. There was a statistically significant increase in tumor neurosphere proliferation, ROS, and mitoDNA content in both TRP and GL261 mouse glioma cells after co-incubation with purified mitochondria versus controls. **Conclusion:** Our work provides insights into neutrophil interactions with the microenvironment via mito-transfer, likely common to many proinflammatory diseases of the CNS.

Disclosures: N. Filippova: None. **J. Shi:** None. **X. Yang:** None. **C. Sorochinsky:** None. **L.B. Nabors:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.02/R3

Topic: B.10. Neuro-Oncology

Support: Mayo Clinic Comprehensive Cancer Center Startup Funds

Title: Characterizing Scinderin as a Regulator of Myeloid Cell Behavior in the Glioblastoma Tumor Microenvironment

Authors: *A. SENKERIK[1], E. HUIE[2], K. BHAT[1];
[1]Mayo Clin., Phoenix, AZ; [2]Mayo Clin. Grad. Sch. of Biomed. Sci., Phoenix, AZ

Abstract: Background: Glioblastoma (GBM) is an aggressive primary brain cancer with a median survival of 15-18 months. To identify novel therapeutics for GBM, we conducted single-cell RNA sequencing of patient-matched peripheral blood mononuclear cells (PBMCs) and tumor-infiltrating immune cells. We identified scinderin (SCIN), a protein-coding gene that regulates the organization of the microfilament network, as highly expressed in myeloid cells, but not PBMCs. Notably, previous studies have linked upregulated SCIN to a poorer prognosis in patients with other cancers, but its role in GBM has yet to be investigated.
Methods: We used immunohistochemistry to validate and quantify SCIN expression on 47 paraffin-embedded human GBM samples. To characterize the role of SCIN expression in myeloid cells, we generated a SCIN-overexpressing THP-1 myeloid cell line and assessed migration, F-actin expression, and phagocytosis. We conducted bulk RNA sequencing to identify pathways associated with SCIN expression.
Results: Single-cell RNA sequencing revealed that SCIN expression is highly enriched in myeloid cells of the GBM tumor microenvironment. Preliminary findings indicate that SCIN expression increases cell migration while reducing F-actin expression and phagocytic activity. Bulk RNA sequencing data revealed transcriptomic differences in high SCIN expression.
Conclusion: These results suggest that SCIN may play a role in GBM progression, though further investigation is needed to clarify its function and potential as a therapeutic target.

Disclosures: A. Senkerik: None. **E. Huie:** None. **K. Bhat:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.03/R4

Topic: B.10. Neuro-Oncology

Support: NIH R01NS121660

Title: Role of microglial infiltration in early symptom onset and progression of epileptogenesis in an immunocompetent mouse model of glioblastoma.

Authors: *D. E. FLETCHER[1], T. VUE[2];
[1]Univ. of New Mexico Sch. of Med., Albuquerque, NM; [2]Dept. of Neurosciences, Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM

Abstract: Glioblastoma (GBM) is the most common, aggressive malignancy of the brain and CNS. GBM represents a significant public health concern due to treatment limitations and poor survival rates. Because GBM cells can disseminate extensively throughout the brain, compressing and altering the structure of surrounding brain regions, clinical manifestations are often delayed or difficult to detect. Consequently, diagnosis frequently occurs at late or advanced stages, which contributes to treatment failure and near universal recurrence. Because of their roles in neuroinflammation and ability to remodel the tumor microenvironment, microglia have been implicated in GBM progression and the development of associated neurological symptoms, including cortical hyperexcitability and seizures. *We hypothesized that microglial infiltration of brain tumors contributes to detectable neurological deficits that could provide opportunities for earlier diagnosis and therapeutic intervention in GBM.* To test this hypothesis, we leveraged an innovative, CRISPR-Cas9 GBM mouse model that recapitulates tumor progression within an intact and translationally relevant immune microenvironment. Brain tumors were induced in Cre-dependent tdTomato reporter for longitudinal behavior and immunohistochemical analyses to correlate microglial infiltration and activation with the onset and severity of neurological symptoms. Specifically, inverted mesh, behavior batteries, accelerated rotarod, Catwalk gait analysis, and continuous PhenoTyper Box monitoring were employed to characterize behavioral symptoms in tumor-bearing and non-tumor littermate control mice at P30, P45, P60, and P75. A separate cohort of mice were used to assess microglial infiltration at these timepoints. We show that tumor mice exhibit significant behavioral alterations compared to controls. Notably, latency to fall was increased in tumor animals at all time points for both inverted mesh and accelerated rotarod behavioral tests. Behavior battery revealed delayed reflexes in tumor mice compared to controls. Additionally, tumor mice showed various motor deficits as early as P45 on the Catwalk and developed seizures and immobility behaviors as early as P60. Importantly, these behavioral abnormalities coincided with the onset of significant microglial infiltration and activation within the tumor core, margin, and surrounding brain regions. Together, these findings suggest that microglia may serve as a potential target for seizure and therapeutic intervention and identifies neurological motor deficits as potential early symptoms for the diagnosis of GBMs.

Disclosures: D.E. Fletcher: None. **T. Vue:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.04/R5

Topic: B.10. Neuro-Oncology

Title: Collagen I-Driven Reactive Astrocyte Reprogramming in Glioblastoma Progression

Authors: *M. HASHEMI, A. COMBA, C. WILLEY, R. MILLER, S. ROBEL;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Glioblastoma (GBM) is the most aggressive primary tumor of the central nervous system and remains incurable due to diffuse invasion into the surrounding brain parenchyma. During invasion, glioma cells engage in dynamic interactions with brain-resident cells, particularly astrocytes, which undergo transcriptional reprogramming into reactive states that influence tumor progression. Recent single-cell and spatial transcriptomics studies have identified the Ast3 reactive astrocyte state as enriched in mesenchymal GBM and associated with therapy resistance and poor clinical outcome. However, the signals that drive Ast3 polarization remain unknown. Because mesenchymal GBMs exhibit extensive ECM remodeling and elevated Collagen I (COL1A1) expression, we investigated whether tumor-derived collagen I promotes Ast3 astrocyte polarization and glioma invasion. Using syngeneic mouse glioma models, we found that COL1A1-high tumors exhibited enhanced mesenchymal ECM programs, increased accumulation of reactive astrocytes at the invasive edge, and reduced survival. RNA-seq analysis of microdissected invasive-edge niches revealed that genetic depletion of tumor-derived COL1A1 suppressed pan-reactive astrocyte genes, including GFAP, CHI3L1, and AQP4, and reduced expression of Ast3-associated and pro-invasive factors, including TGFBR2, WWTR1 (TAZ), TNC, LOXL2, ADAM12, TIMP1, PDPN, and ANXA2. Analysis of human GBM specimens confirmed enrichment of Ast3 transcriptional programs in COL1A1-high tumors. Integrative network analysis identified ITGB1, encoding the common β1-subunit of collagen-binding integrins, as a central regulatory hub associated with Ast3 gene expression. Consistently, Col1a1 depletion reduced expression of the collagen receptor subunits Itga1 and Itgb1, while quantitative immunofluorescence demonstrated that 29.4% of GFAP-positive astrocytes at the invasive front co-expressed ITGB1. Together, these findings support a model in which tumor-derived collagen I promotes astrocyte polarization toward the Ast3 state through integrin-associated signaling, suggesting a feed-forward invasive niche that facilitates glioma progression. These studies identify a previously unrecognized ECM-astrocyte signaling axis and nominate collagen-dependent astrocyte reprogramming as a potential therapeutic target in GBM.

Disclosures: M. Hashemi: None. **A. Comba:** None. **C. Willey:** None. **R. Miller:** None. **S. Robel:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.05/R6

Topic: B.10. Neuro-Oncology

Support: Weekly Family Cancer Neuroscience Fellowship

Title: Serotonergic signaling in high-grade glioma: electrophysiological evidence for bidirectional communication

Authors: *M. VON GUNTEN;
Stanford Univ., Stanford, CA

Abstract: High-grade gliomas (HGGs) engage in bidirectional interactions with neural circuits that promote tumor progression. Although glutamatergic and GABAergic activity strongly drive glioma growth, data is now emerging that demonstrates that certain neuromodulatory systems also play a role in driving tumor progression. Recent work demonstrates that serotonergic activity enhances glioma proliferation through activation of 5-HT2A receptors expressed on glioma cells, while gliomas in turn alter serotonergic neuronal activity and increase serotonin release within the tumor microenvironment. Furthermore, glioma-bearing mice showed changes in forced swim and sucrose preference tests, behavioral assays that are sensitive to modulation of serotonergic systems. However, the electrophysiological mechanisms underlying glioma-induced changes in serotonergic neuron function and serotonin-induced glioma growth have not been fully characterized.
To address this knowledge gap, we performed whole-cell and cell attached electrophysiological recordings in patient-derived xenograft models of high-grade gliomas. Glioma-bearing mice exhibited increased spontaneous firing rates and a greater proportion of spontaneously active serotonergic neurons compared to sham controls. Exogenous serotonin evoked slow inward currents in glioma monoculture cells consistent with GPCR-mediated signaling, which were blocked by the 5-HT2A receptor antagonist pimavanserin. In xenografted acute slice preparations, bath application of serotonin also increased the amplitude of voltage-gated calcium channel-mediated currents.
Together, these findings demonstrate glioma-induced changes in dorsal raphe neuron activity and identify molecular mechanisms through which serotonin affects glioma electrophysiology, highlighting possible therapeutic targets.

Disclosures: M. Von Gunten: None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.06/S1

Topic: B.10. Neuro-Oncology

Support: Pelotonia Institute for Immuno-Oncology (PIIO) at The Ohio State University Comprehensive Cancer Center (OSUCCC)
The Mary Elaine Johnson Neuro-Oncology Fund
The Neuro-Oncology Novel Therapies and Research Fund.

Title: Glioblastoma Reprograms Nociceptors to Drive Myeloid Suppression

Authors: *S. KARTHIK[1,3], O. SANTIAGONUNEZ AHUMADA[1,3], S. ASALLA[1,3], Y. WANG[1], K. KAUR[1,3], S. GHIMIRE[1,3], P. GIGLIO[1], A. TEDESCHI[4,2], N. ACHARYA[1,3];

[1]Dept. of Neurol., [2]Chronic Brain Injury Program, The Ohio State Univ., Columbus, OH; [3]Pelotonia Inst. for Immuno-Oncology, OSUCCC – James, The Ohio State Univ., Columbus, OH; [4]Dept. of Neurosci., Wexner Med. Center, The Ohio State Univ., Columbus, OH

Abstract: Background: Glioblastoma(GBM)remainsrefractory to immunotherapybecause of animmunosuppressive,myeloid-dominatedtumor microenvironment.The meningesare denselyinnervatedby trigeminalganglion(TG)nociceptorswhose axons interfacewithimmunecompartments, suggestingperipheralsensory circuitsinfluenceCNS tumor immunity. WhetherGBM engages nociceptorsignalingto reinforceimmunesuppressionremainsunknown. Wehypothesizedthat GBM co-opts TG nociceptorsignalingto promote macrophage-mediatedimmunesuppressionthrough a CGRP–RAMP1 axis.**Methods:** Female WT C57BL/6 micewere orthotopicallyimplantedwithCT2A or SB28 gliomacells, or sham-operated (n=3 biologicalreplicates/group).IpsilateralTGs were harvested 15 dpost implantation(p.i).and immunostainedfor CGRP and c-Fos. Fluorescence intensityECDFs(~200–300neurons/condition)were compared usinga Bonferroni-correctedthree-sampleKolmogorov–Smirnovtest (**$p<2.2 \times 10^{-16}$).Resiniferatoxin(RTX)-mediatednociceptorablationwas performed by stereotacticTG injectioninto4-week-old female WT C57BL/6 mice(n=7),followed by intracranialCT2A implantationand anti–CTLA-4therapy, where survivalwas assessed by Kaplan–Meieranalysis.To test CSF-mediatedactivation,naïve TG neuronswere cultured ex vivowithCSF from GBM-bearingor sham micefor 40 h and analyzed byqPCR for Calca, Atf3, Jun, and Sox11 (n=5–9),or by Fluo-4 AM calciumimaging,Tuj1(βIII-tubulin)ICC, and CGRP ICC intriplicateexperiments(~105neurons/condition).WT or$Ramp1^{-/-}$ BMDMs were cultured withsupernatants from control or GBM-elicitedTG neuronsand assessed by Arg1 ICC 72 h post-treatment.**Results:** TG from CT2A- and SB28-bearingmiceexhibitedsignificantrightwardshiftsinc-Fosand CGRP fluorescence intensitydistributionsrelativeto sham controls. Nociceptorablationprolonged survivaland rendered an immunotherapy-resistantGBM model intoone responsivetoanti–CTLA-4.CSF from GBM-bearingmiceincreasedaxon length, calciuminflux,CGRPexpression,and injury/plasticitygenes. Macrophages exposed to supernatants fromGBM-elicitedneurons upregulated Arg1, while$Ramp1^{-/-}$ BMDMs stayed comparable tocontrols, implicatingTG neuron-derivedCGRP–RAMP1 signalinginimmunosuppressivemacrophage polarization.**Conclusions:** GBM reprograms TG nociceptorsintoa CGRP-highstate. Disruptingnociceptorsignalingprolongs survivaland restores immunotherapyresponsiveness,revealinga previouslyunrecognizedneural checkpointgoverningtumor immunityinGBM. Mechanistically, aCGRP–RAMP1 neuroimmuneaxispromotes macrophage immunesuppression.

Disclosures: S. Karthik: None. **O. Santiagonunez Ahumada:** None. **S. asalla:** None. **Y. Wang:** None. **K. Kaur:** None. **S. Ghimire:** None. **P. Giglio:** None. **A. Tedeschi:** None. **N. Acharya:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.07/S2

Topic: B.10. Neuro-Oncology

Support: Baillet Latour Funds-ZHU E0642
Fondation contre le Cancer, Belgium (grant no. F/2024/2681)

Title: Unlocking the Anti-Tumor Potential of α2-Adrenergic Receptor Agonists

Authors: *J. ZHU;
Ludwig Inst. for Cancer Research, de Duve Institute, UCLouvain, Brussels, Belgium

Abstract: Emerging evidence suggests that neural signaling pathways play fundamental roles in regulating immune responses, yet the mechanisms linking neurotransmitter receptors to anti-tumor immunity remain poorly understood. Here, we identify alpha2-adrenergic receptor (alpha2-AR) signaling as a potent neuroimmune pathway that controls macrophage function and promotes effective anti-tumor immune responses.Using multiple murine tumor models, including tumors resistant to immune checkpoint blockade, we found that activation of alpha2-AR signaling by clinically available agonists induced robust tumor regression and prolonged survival. Therapeutic efficacy was entirely dependent on an intact immune system and required host expression of alpha2A-AR, indicating that adrenergic signaling acts through immune rather than tumor cells. Similar effects were observed in humanized mouse models, supporting translational relevance.To define the underlying neuroimmune mechanisms, we combined genetic models, immune cell depletion, and single-cell transcriptomic profiling. alpha2-AR activation remodeled the tumor microenvironment, increasing T-cell infiltration while reducing immunosuppressive myeloid populations. Single-cell analyses revealed broad activation of innate and adaptive immune programs, particularly within macrophages and T lymphocytes. Functional studies demonstrated that macrophages serve as the primary cellular target of alpha2-AR signaling, acquiring enhanced capacity to activate CD4+ and CD8+ T-cell responses. Loss of alpha2A-AR signaling abolished these effects, establishing a critical role for adrenergic receptor-dependent immune regulation.These findings uncover a previously unrecognized mechanism by which adrenergic signaling shapes immune function and tissue surveillance. By demonstrating that activation of a classical neurotransmitter receptor can reprogram macrophage activity and drive protective T-cell responses, this work provides new insight into neuroimmune communication and highlights adrenergic pathways as promising therapeutic targets for immune-mediated diseases.

Disclosures: J. Zhu: None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.08/S3

Topic: B.10. Neuro-Oncology

Title: The noradrenergic Locus Coeruleus modulates mammary tumor progression and immune infiltration

Authors: *N. C. HOLLAND[1], L. BOYD[4], A. BERISHA[2], L.-J. CASEÑAS[5], J. C. BORNIGER[3];
[1]Cold Spring Harbor Lab., Astoria, NY; [2]Neuroscience/ Cancer, [3]Neuroscience/Cancer Ctr., Cold Spring Harbor Lab., Cold Spring Harbor, NY; [4]Univ. of Connecticut, Storrs Mansfield, CT; [5]Rockefeller Univ., New York, NY

Abstract: Neurite activity in the breast cancer tumor microenvironment (TME) influences inflammatory tone and tumor progression. These neurites are part of the peripheral nervous system and relay information to, and from the brain, yet neuronal populations in the brain that influence TME neuron activity are not characterized. Here, we used polysynaptic retrograde tracing from E0771 primary syngeneic mammary tumors to identify populations in the brain connected to TME neurons. We combined tracing with pseudorabies virus (PRV) whole-brain immunofluorescence with iDISCO clearing of the thoracic spine and lightsheet imaging to simultaneously visualize the tumor-innervating neurons of the peripheral nervous system and their inputs from the brain. We find that PRV is expressed strongly in the noradrenergic locus coeruleus (LC-NE), suggesting a polysynaptic connection to neurons that innervate the TME. High tonic LC-NE population activity is closely associated with increased wakefulness, stress, and sympathetic tone. To observe the relationship between tonic LC-NE activity and tumor progression, we obtained 24-hour fiber photometry recordings at the LC-NE in unperturbed E0771-bearing mice throughout tumor development. We found that higher levels of tonic LC-NE activity prior to, and during progression, correlate with larger final tumor volumes, and that high levels of LC-NE activity prior to tumor implantation could predict final tumor size. This suggested a positive relationship between progression and tonic LC-NE activity. To measure the effect of high tonic LC-NE activity on E0771 tumors, we administered daily tonic frequency optogenetic stimulation of LC-NE and monitored tumor progression. LC-NE stimulation accelerated E0771 tumor development, resulting in larger lesions. Flow cytometry and single-cell RNA sequencing of tumors from LC-NE-stimulated mice revealed a significantly reduced macrophage presence in the TME and upregulation of inflammatory transcripts. Specific ablation of LC-NE was sufficient to slow tumor progression, while daily administration of a non-specific LC-NE inhibitor, clonidine, did not, suggesting prolonged and specific silencing of LC-NE is required to slow tumor progression. These findings implicate LC-NE as a modulator of breast cancer progression and immune infiltration, and link central arousal circuitry to inflammatory dynamics in murine breast cancer.

Disclosures: N.C. Holland: None. **L. Boyd:** None. **A. Berisha:** None. **L. Caseñas:** None. **J.C. Borniger:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

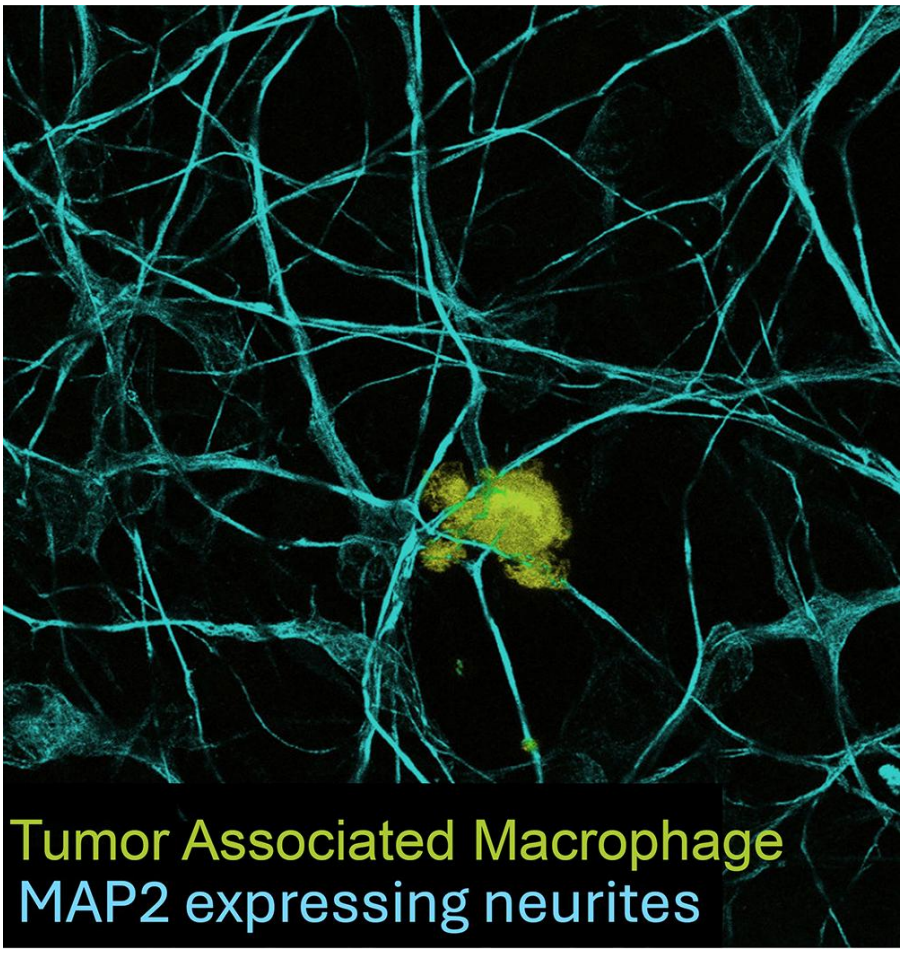
Program #/Poster #: PSTR217.09/S4

Topic: B.10. Neuro-Oncology

Title: Tumor-associated macrophages establish a noncanonical macrophage-neuron interface that promotes tumor innervation through SPP1-mTORC2 signaling

Authors: *F. BIFARI;
Univ. of Milan, Segrate, Milan, Italy

Abstract: Neurons interact with non-neuronal cells through communication mechanisms that extend beyond classical synaptic transmission. In tumors, this heterocellular communication may contribute to the formation of an innervated niche, yet the immune-cell programs that instruct tumor-associated nerve growth remain poorly defined. Recently, we identified a distinct nerve growth-associated signature in tumor-associated macrophages (TAMs), revealing that macrophages within the tumor microenvironment can directly influence neural remodeling (Dolci et al. Immunity 2026). TAMs promoted neurite outgrowth in neuronal cultures and enhanced nerve growth within tumors, indicating that macrophage-derived signals are sufficient to support tumor innervation. Mechanistically, we identified SPP1 as a required mediator of TAM-driven neural growth. SPP1 activated neuronal Rictor/mTORC2 signaling, and interference with this pathway reduced the neurotrophic activity of TAMs. These findings define a noncanonical macrophage-neuron interface in which tumor-educated immune cells instruct neuronal growth through soluble signaling. By linking macrophage wound-healing programs to tumor innervation, this work expands the concept of tumor-neuron crosstalk and identifies the SPP1-mTORC2 axis as a candidate mechanism by which the immune microenvironment shapes neural remodeling in disease. Our results support the idea that neuronal architecture in pathological tissues is not only determined by neuron-intrinsic programs, but also by dynamic communication with non-neuronal cells.



Disclosures: F. Bifari: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HEMERA s.r.l.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.10/S5

Topic: B.10. Neuro-Oncology

Support: NINDS- NS105796

Title: Nerve injury promotes peripheral nerve sheath tumorigenesis through axon-dependent YAP/TAZ activation in Schwann cells

Authors: *B. YU[1,2], H. KIM[3], Y.-J. SON[3];
[1]Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA; [2]Dept. of Neural Sci., Dept. of Neural Sciences, Lewis Katz Sch. of Medicine, Temple Univ., Phliadelphia, PA; [3]Dept. of

Neural Sci., Dept. of Neural Sciences, Lewis Katz Sch. of Medicine, Temple Univ., Philadelphia, PA

Abstract: Peripheral nerve tumors arise within a specialized axon-Schwann cell microenvironment, and prior work in NF1 models indicates that nerve injury can convert adult peripheral nerve from a tumor-suppressive to a tumor-promoting state. However, how injury-induced changes in the nerve microenvironment accelerate tumorigenesis remains poorly understood. Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are Hippo pathway effectors implicated in MPNST, and our previous work showed that axon-Schwann cell interactions regulate Schwann cell YAP/TAZ. We tested the exploratory hypothesis that nerve injury and axon regeneration accelerate tumorigenesis by driving pathological YAP/TAZ activation in Lats1/2-deficient Schwann cells. Lats1/2 was inducibly deleted in Schwann cells of young adult male and female Plp1-CreER;Lats1$^{fl/fl}$;Lats2$^{fl/+}$ mice. Intact sciatic nerves, crushed nerves that permit axon regeneration, and transected nerves in which axon regeneration was prevented were compared with littermate controls and contralateral intact nerves. Each experimental group included more than six mice, and image analyses were performed blinded to genotype and injury condition. In intact Lats1/2-deficient nerves, YAP/TAZ immunoreactivity was only modestly increased and nerve architecture remained largely preserved during the early post-deletion period. In contrast, sciatic nerve crush caused rapid nerve enlargement and MPNST-like peripheral nerve sheath tumor formation in Lats1/2-deficient nerves within 2-9 weeks, whereas contralateral intact nerves and injured control nerves did not show comparable pathology. Immunostaining showed strong YAP/TAZ upregulation in Sox10-positive Schwann cells in crushed Lats1/2-deficient nerves, accompanied by abnormal cellular expansion, while axonal and myelin markers confirmed axon regeneration through the distal injured nerve. Strikingly, when axon regeneration was blocked by nerve transection, Lats1/2-deficient distal nerves failed to develop MPNST-like tumors and Schwann cells lacked robust YAP/TAZ expression. These findings indicate that nerve injury markedly accelerates MPNST-like peripheral nerve sheath tumorigenesis in genetically susceptible Schwann cells, but that this effect requires axonal presence or regeneration. Together, our results identify axon-dependent Schwann cell YAP/TAZ activation as a mechanism linking nerve injury to rapid peripheral nerve sheath tumorigenesis.

Disclosures: B. Yu: None. **H. Kim:** None. **Y. Son:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.11/S6

Topic: B.10. Neuro-Oncology

Support: PNRR
HERMES FET-HORIZON 2020

Title: Tumor associated macrophages promote neural tissue regeneration after severe contusive compressive spinal cord injury

Authors: *I. DECIMO;
Univ. of Verona, Verona, Italy

Abstract: Repair after spinal cord injury requires coordinated communication between neurons and non-neuronal cells that can reshape the inflammatory, vascular, extracellular matrix, and glial environment of the lesion. Building on the identification of a nerve growth-associated program in tumor-associated macrophages (TAMs), we tested whether this macrophage-derived pro-neural activity could be redirected toward CNS repair (Dolci et al Immunity 2026). In a severe complete compressive-contusive spinal cord injury model, adoptive transfer of TAMs induced a broad reparative response at the lesion site. Treatment promoted neuronal survival, axonal regrowth, myelination, vascular remodeling, extracellular matrix reorganization, and immune modulation, collectively converting the injured spinal cord microenvironment into a more permissive niche for tissue repair. These structural changes were associated with partial motor recovery. Mechanistically, TAM promoted neurite outgrowth in through SPP1-dependent activation of neuronal Rictor/mTORC2 signaling. Long-term preclinical evaluation showed no tumor formation and no major histopathological alterations in spinal cord or visceral organs. Together, these data indicate that macrophage-neuron communication can be harnessed to promote multimodal spinal cord regeneration. This work supports a broader view of CNS repair in which recovery is driven by noncanonical interactions between neurons and immune cells.

Disclosures: I. Decimo: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HEMERA s.r.l..

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.12/S7

Topic: B.10. Neuro-Oncology

Support: American Brain Tumor Association Jack and Fay Netchin Medical Student Summer Fellowship Grant
NIH/NCI R01CA276942
NIH/NINDS R21NS123685
American Cancer Society Research Scholar Grants RSG-19-185-01-MPC
Cancer Prevention and Research Institute of Texas RP200615 and RP250557
NIH R03 CA252770

Title: Enhancing Viro-Immunotherapy in Glioblastoma Through microRNA-Mediated Senolysis

Authors: *S. M. BEAN[1], J. KIM[2,1], M. HUANG[3,1], M. NOH[1], A. MILLER[1], L. NGUYEN[1], T. LEE[1,4], J. YOO[1];

[1]Vivian L. Smith Dept. of Neurosurg., McGovern Med. School, Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Stony Brook Univ., Middle Island, NY; [4]MD Anderson Cancer Ctr. UTHealth Grad. Sch. of Biomed. Sci., Houston, TX

Abstract: Enhancing Viro-Immunotherapy in Glioblastoma Through microRNA-Mediated Senolysis

Stephanie Bean[1#], Jiyeon Kim[1#], Minxin Huang[1], Ji Young Yoo[1,2*] and Tae Jin Lee[1,2*] [1]Vivian L. Smith Department of Neurosurgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas, 77030, USA, [2]MD Anderson Cancer Center UTHealth Graduate School of Biomedical Science, Houston, Texas, 77225, USA

Background: Glioblastoma (GBM) is among the most aggressive primary brain tumors. Conventional therapies largely aim to induce apoptosis, but efficacy is limited because cancer cells often escape apoptosis by entering senescence. In addition, apoptosis rarely triggers immunogenic cell death, failing to effectively harness the benefits of immunotherapy. Inducing cell death in the senescent cancer cells can lead to immunogenic senolysis. Oncolytic herpes simplex virus-1 (oHSV) can cause tumor-specific immunogenic necrosis, representing an attractive alternative strategy to induce senolytic cancer cell death. Yet GBM exhibits intrinsic and extrinsic resistance to oHSV therapy. We identified miR-433-3p as a putative tumor-suppressive microRNA, which sensitizes GBM tumors to oHSV therapy by inducing senescence-like cell cycle arrest.Hypothesis: We hypothesize that inducing senescence in tumor cells with miR-433-4p will increase immunogenic senolysis after oHSV treatment, improving the effectiveness of viro-immunotherapy in GBM.Aims: We aim to investigate the molecular mechanism by which miR-433-3p-induced senescence sensitizes tumor cells to oHSV and facilitates immunogenic senolysis.Methods: Primary GBM cells and glioma cell lines were used for mechanisms, senescence induction, viral replication, cell viability, and in vivo studies. Results: miR-433-3p overexpression induced senescence-like cell cycle arrest through direct inhibition of FYN expression, an upstream regulator of Akt signaling pathway, but sustained protein synthesis machinery. Combination therapy demonstrated enhanced oHSV replication and cytotoxicity.Conclusion: miR-433-3p sensitizes GBM to oHSV, promoting immunogenic senolysis and synergistic tumor cell killing. It highlights itself as a promising therapeutic target for the development of a novel combinatorial strategy to overcome oHSV resistance and improve GBM patient outcomes.

Disclosures: S.M. Bean: A. Employment/Salary (full or part-time):; UTHealth 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.; American Brain Tumor Association Jack and Fay Netchin Medical Student Summer Fellowship Grant. **J. Kim:** A. Employment/Salary (full or part-time):; UTHealth Houston. **M. Huang:** A. Employment/Salary (full or part-time):; UTHealth Houston. **M. Noh:** A. Employment/Salary (full or part-time):; UTHealth 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.; CPRIT Postdoctoral Fellows in the Biomedical Informatics, Genomics and Translational Cancer Research Training Program (BIG-TCR) Cancer Prevention & Research Institute of Texas (CPRIT: RP210045). **A. Miller:** A. Employment/Salary (full or part-time):; UTHealth 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.; American Legion Auxiliary Fellowship in Cancer Research. **L. Nguyen:** A. Employment/Salary (full or part-time):; UTHealth Houston. **T. Lee:** A. Employment/Salary (full or part-time):; UTHealth 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.; NIH R03 CA252770, Cancer Prevention and Research Institute of Texas RP200615 and RP250557, American Cancer Society Research Scholar Grants RSG-19-185-01-MPC, NIH/NINDS R21NS123685, NIH/NCI R01CA276942. **J. Yoo:** A. Employment/Salary (full or part-time):; UTHealth 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.; NIH/NCI R01CA276942-01A1S1, NIH/NINDS R21NS123685, American Cancer Society Research Scholar Grants RSG-19-185-01-MPC.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.13/S8

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant T32CA257923
NIH Grant P30CA247796
NIH Grant R01CA293376
NIH Grant R01NS111033

Title: Radial glial cell-derived antigens reveal a developmental strategy for targeting glioblastoma

Authors: *C. LOVE[1], J. FIGG[2], I. WEST[2], D. JIN[2], A. HACHE[2], K. LONG-JAMES[2], A. WILLIAMS[2], G. MOORE[2], C. FLORES[2];
[1]Neurosci., [2]Neurosurg., Univ. of Florida, Gainesville, FL

Abstract: Glioblastoma (GBM) remains refractory to immunotherapy due to intratumoral heterogeneity, immune escape, and persistence of stem-like tumor populations. Many of these therapy-resistant states resemble developmental programs active during brain formation, including programs associated with radial glial cells (RGCs), transient early progenitors that support cortical growth, self-renewal, migration, and neuro-glial lineage specification. Because RGC-like cellular states re-emerge in GBM but are largely absent from healthy adult brain, we hypothesized that RGCs could serve as a renewable, tumor-independent antigen source for adoptive cellular therapy (ACT) in GBM. Cultured RGCs shared conserved transcriptional programs with murine GBM models while remaining distinct from healthy adult cortex. Shared transcripts were enriched for pathways associated with cell cycling, extracellular matrix

organization, migration, and neuro-glial identity, consistent with developmental programs that may support malignant plasticity. Ex vivo expanded T cells generated using RGC-derived RNA (rgcRNA) produced predominantly $CD8^+$ effector-memory T cells comparable to positive control total tumor RNA(ttRNA)-derived T cells. Functionally, rgcRNA T cells exhibited broad glioma reactivity, producing IFNγ and mediating cytotoxicity against KR158B and GL261 gliomas, while ttRNA T cells had restricted activity to tumor-of-origin. In orthotopic glioma-bearing mice, rgcRNA-ACT significantly prolonged survival and achieved efficacy comparable to ttRNA-ACT. This effect was not observed against intracranial EO771 breast tumors, supporting specificity for glioma-associated developmental programs rather than nonspecific intracranial tumor killing. To model spatial tumor-immune interactions, we used 3D bioprinted assays containing stem-like and invasive tumor populations. In this system, rgcRNA T cells preferentially migrated toward and killed stem-enriched tumor compartments marked by CD133, CD15, and PTPRZ1, suggesting that RGC-derived antigens direct T cells toward malignant cellular states linked to recurrence and invasion. Human GBM analyses further showed that RGC-associated stem and invasion markers were present in primary tumors and enriched in recurrent disease. Finally, human rgcRNA T cells were more effective at killing recurrent tumor cells than primary tumor cells when compared to pp65 control T cells. Together, these findings identify RGCs as a renewable developmental antigen source and support an ontogeny-guided immunotherapeutic strategy for targeting self-renewing, stem-like, and invasive cellular states in GBM.

Disclosures: C. Love: None. **J. Figg:** None. **I. West:** None. **D. Jin:** None. **A. Hache:** None. **K. Long-James:** None. **A. Williams:** None. **G. Moore:** None. **C. Flores:** A. Employment/Salary (full or part-time):; iOncologi.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.14/Web Only

Topic: B.10. Neuro-Oncology

Support: NIEHS (P30ES030283, JC for pilot grant)
Kentucky Pediatric Cancer Research Trust Fund Grants (2300001625, 2400001295, and 2400001542, JC and MF).

Title: Early-Life Cadmium Exposure Reprograms Hematopoietic Landscapes and Attenuates CAR T-Cell Efficacy in Pediatric High-Grade Glioma

Authors: *W. ZENG[1], M. TAN[1], B. YANG[1], J. MROCZKOWSKA[1], M. FERGUSON[1,2], J. CAI[1,2];
[1]Pediatrics, Univ. of Louisville Sch. of Med., Louisville, KY; [2]Norton Children's Cancer Institute, Norton Healthcare, Louisville, KY

Abstract: Background: Pediatric brain and CNS tumors have surpassed leukemia as the primary cause of cancer-related mortality in children, with particularly high incidence rates in Kentucky. While CAR T-cell therapy offers a promising therapeutic avenue, its efficacy is limited by the immunosuppressive tumor immune microenvironment (TIME). Environmental stressors, specifically cadmium (Cd), are prevalent in Kentucky through soil contamination and tobacco use, yet their role in immune reprogramming and pediatric oncology remains poorly defined. **Methods:** We utilized C57BL/6J and humanized NSG-SGM3 mouse models exposed to perinatal low-dose Cd (0.5 and 5 ppm). Immune profiling was conducted via CyTOF and mass spectrometry. We further established an orthotopic xenograft model of diffuse intrinsic pontine glioma (DIPG) to evaluate the impact of Cd on B7H3-targeted CAR T-cell therapy and the cellular constitution of the TIME. **Results:** Blood Cd levels in 5 ppm-exposed mice (1.48-2.14 μg/L) accurately modeled human secondhand smoke exposure. We observed systemic hematopoietic shifts characterized by 30% -50% B-cell loss and a 3- to 6-fold myeloid expansion across both sexes. In the bone marrow, 5 ppm Cd induced a sex-divergent depletion of effector CD4+/CD8+ T cells and mature NK cells. Functionally, early-life Cd exposure significantly accelerated DIPG progression, driving a high-Ki67 proliferative phenotype. Crucially, the anti-tumor efficacy of B7H3-targeted CAR T cells was significantly attenuated in Cd-exposed cohorts. **Conclusion:** These data demonstrate that early-life Cd exposure induces a 'primed' inflammatory state and lymphoid attrition, creating a TIME inherently resistant to advanced cellular therapies. This study highlights the critical need to account for environmental toxicant exposure in the development of precision immunotherapies for pediatric high-grade gliomas. Future efforts will utilize autologous-like humanized models to further dissect the molecular mechanisms of Cd-induced therapeutic resistance.

Disclosures: W. Zeng: None. **M. Tan:** None. **B. Yang:** None. **J. Mroczkowska:** None. **M. Ferguson:** None. **J. Cai:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.15/Web Only

Topic: B.10. Neuro-Oncology

Support: NIEHS (P30ES030283, JC for pilot grant)
Kentucky Pediatric Cancer Research Trust Fund Grants (2300001625, 2400001295, and 2400001542, JC and MF)

Title: Low-Dose Cadmium Exposure Triggers Epigenetic Dysregulation and Accelerates Orthotopic Tumorigenesis in Pediatric Glioblastoma

Authors: B. YANG[1], W. ZENG[1], M. TAN[1], J. MROCZKOWSKA[1], M. FERGUSON[1,2], *J. CAI[1,2];

[1]Pediatrics, Univ. of Louisville Sch. of Med., Louisville, KY; [2]Norton Children's Cancer Institute, Norton Healthcare, Louisville, KY

Abstract: Background: Pediatric high-grade glioma (pHGG) development is linked to environmental factors and gene-environment interactions. The heavy metal cadmium (Cd) bioaccumulates via pollution, diet, and tobacco smoke, yet its influence on pHGG malignant progression remains unclear. This study evaluates how low-dose Cd exposure modulates epigenetic regulatory pathways and drives tumor progression using in vitro and in vivo pediatric glioblastoma models. **Method:** Human pediatric glioblastoma SF188 cells were treated with Cd (0, 0.05, 0.5, 5 ppm) for 24-72 hours. Viability was evaluated via MTT assays. Transcriptional and protein alterations were quantified via qPCR and Western blot, respectively. In vivo oncogenic potential was assessed using an orthotopic xenograft mouse model implanted with SF188 cells following pre- and early postnatal Cd exposure. Intergroup variations were analyzed via one-way analysis of variance (ANOVA) paired with Tukey's post-hoc analysis, defining statistical significance at $p<0.05$. **Results:** Cd exposure induced dose-dependent effects on SF188 cell viability. Gene expression analysis revealed that both 0.5 and 5 ppm Cd exposures significantly upregulated anti-apoptotic *BCL2L1*, immune checkpoint *B7H3*, and DNA repair gene *BRCA1* ($p< 0.05$), whereas *PD-L1* expression increased markedly only at the 5 ppm threshold. Cd exposure at 0.5 ppm initially upregulated *SUZ12* and *EZH1/2* transcripts at 48 hours ($p<0.001$), but prolonged 72-hour exposure to 0.5 and 5 ppm significantly suppressed these core Polycomb Repressive Complex 2 (PRC2) components ($p<0.0001$). Western blots confirmed reduced SUZ12 and EZH2 protein levels. Parallel to this restricted PRC2 phenotype, 5 ppm Cd significantly elevated histone H3K27 monomethylation (H3K27me1) and dimethylation (H3K27me2), while trimethylation (H3K27me3) remained stable. *In vivo*, prenatal and early postnatal exposure to 5 ppm Cd significantly increased tumorigenesis incidence and accelerated tumor progression in orthotopic xenografts. **Conclusion:** Low-dose environmental Cd exposure profoundly disrupts the epigenetic landscape by suppressing core PRC2 components and altering the H3K27 methylation profile. This epigenetic rewiring occurs alongside induced DNA repair pathways and immune evasion markers, ultimately driving enhanced tumorigenesis and malignancy *in vivo*.

Disclosures: B. Yang: None. **W. Zeng:** None. **M. Tan:** None. **J. Mroczkowska:** None. **M. Ferguson:** None. **J. Cai:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.16/T1

Topic: B.10. Neuro-Oncology

Title: Human cerebral organoids reveal diverse GBM calcium responses to extracellular ATP

Authors: *G. OMANA SUAREZ[1], K. LAWRENCE[2], W. LU[1], T. KANEKIYO[4], H. GUERRERO CAZARES[3];
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Abstract: Neural activity is shaped not only by neurons, but also by glial and disease-associated cells that sense and respond to extracellular signals. Glioblastoma (GBM) is a highlyaggressive brain tumor frequently associated with seizures, yet the cellular events linkingthe tumor microenvironment to abnormal brain excitability remain incompletelyunderstood. Extracellular ATP is released during neural activity, tissue stress, andinflammation, making purinergic signaling a potential bridge between tumor biology andcircuit dysfunction. Here, we asked whether ATP directly alters calcium dynamics in GBMcells growing within a human brain-like environment. Patient-derived GBM cellsexpressing the calcium indicator GCaMP6s were engrafted into 5-month-old iPSC-derived human cerebral organoids. The GBM engraftment into these organoids wascharacterized and two-photon microscopy was used to image for 10 min before and 10min after ATP application. Calcium activity was quantified as ΔF/F relative to the pre-ATP baseline. ATP evoked heterogeneous calcium responses in GBM cells, including transient, sustained, delayed, pulsatile, and weak/nonresponsive patterns. Theseresponse classes were observed across organoids and mapped to distinct spatialregions, suggesting that GBM cells are not uniform sensors of extracellular ATP.Together, these findings show that human organoid models can capture diverse tumor-cell calcium responses to a neuromodulatory extracellular signal. This platform providesa foundation for testing how tumor cells and purinergic signaling pathways contribute toGBM-associated hyperexcitability and seizures.

Disclosures: G. Omana Suarez: None. **K. Lawrence:** None. **W. Lu:** None. **T. Kanekiyo:** None. **H. Guerrero Cazares:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.17/T2

Topic: B.10. Neuro-Oncology

Support: TEDCO30065161

Title: Functional single-cell tracking of glioblastoma heterogeneity with an integrated identity, cell-cycle, and calcium reporter

Authors: *M. MAMO[1], J. WANG[2], Y. LIANG[2];
[1]Univ. of Maryland Baltimore, Baltimore, MD; [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Glioblastoma (GBM) remains one of the most aggressive adult primary brain tumors, with recurrence and therapeutic resistance driven in part by cellular heterogeneity. Single-cell

RNA sequencing, flow cytometry, and endpoint histology have defined GBM cell subpopulations, but these approaches do not resolve how individual tumor cells behave in living systems. Failing to show how the GBM cells dynamically coordinate identity, cell-cycle, calcium activity, migration and outcome over time. To address this gap, we developed ICyCam, an integrated identity, cell-cycle, and calcium reporter for longitudinal functional tracking of mouse glioblastoma cells. ICyCam combines a nuclear BFP-mCherry FUCCI cell -cycle reporter, the cytosolic genetically encoded calcium indicator jRGECO1a, and cytosolic photoactivatable green fluorescent protein (PA-GFP). Distinct subcellular localization and spectral separation enabled simultaneous readout of cell-cycle phase, calcium signaling and photolabeled cell position in GL261 and CT2A murine glioblastoma cells. In cultured cells, ICyCam preserved separable reporter signals, supported repeated imaging of single-cell calcium activity and cell-cycle progression, and enable photoactivation-based tracking of individual cell migration and fate. These data validate ICyCam as multifunctional reporter for resolving functional heterogeneity in mouse GBM models. By linking proliferative state, calcium dynamics, migration, and outcome in the same cells, ICyCam provides a platform to identify dynamic behaviors that may contribute to GBM recurrence and treatment resistance.

Disclosures: M. Mamo: None. **J. Wang:** None. **Y. Liang:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.18/T3

Topic: B.10. Neuro-Oncology

Support: NIH 1R35GM156968
Elsa U. Pardee Foundation

Title: Bioluminescent Kinase Sensors for the detection of growth factor signaling

Authors: *M. P. CHATTERTON[1], E. D. PETERSEN[2], J. ROSSIGNOL[3], J. BAKKE[4], O. DUBEY[5], K. TAYLOR[6];
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Abstract: Growth factor signaling is a crucial component of numerous cellular processes, including metabolism, differentiation, proliferation, neural plasticity, and migration. When growth factor signaling is altered, it can lead to pathologies like cancer cells forming and proliferating within the body, such as glioblastoma multiforme (GB). In this study, we focus on investigating and proposing novel tools to monitor growth factor signaling and use for therapeutic approaches utilizing genetically encoded Bioluminescent Kinase Sensors (BlinKS) to

respond to growth factor signaling via kinases in the epidermal growth factor receptor (EGFR) signaling pathway. Specifically, this study is targeting the kinases within the MEK, RAS, and RAF signaling pathways. We developed a rational library of BlinKS variants with altered phospho-amino acid binding domains (PAABDs) as well as varying kinase substrate peptides and permutations of the linker regions, either flexible or rigid at the protein fusion sites. We tested our BlinKS constructs in U87 glioblastoma cells expressing our candidate sensor variants, treated the cells with epidermal growth factor (EGF), and measured the response of the BlinKS sensors through light emitted by the sensor. Bioluminescence readings were conducted on a plate reader, and it was found that the cells treated with EGF produced more luminescence than those not treated with EGF. We also paired our BlinKS constructs with a light-sensitive transcription factor to create a growth factor-dependent genetic circuit, in this case driving expression of a fluorescent reporter. We found that those treated with EGF produced higher relative fluorescent units than those not treated with EGF. We aim to test these sensors in a variety of neuroscience applications. This includes reporting glioblastoma tumor growth factor signaling and using the sensors to control transcription of therapeutic protein that will inhibit growth to rein in unregulated tumor growth.

Disclosures: M.P. Chatterton: None. **E.D. Petersen:** None. **J. Rossignol:** None. **J. bakke:** None. **O. Dubey:** None. **K. Taylor:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.19/T4

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

Title: Decoding Cellular Communication Networks in Glioblastoma Using Nanoscale Expansion Microscopy

Authors: *S. LEE, J. KANG;
Wertheim UF Scripps Inst., Jupiter, FL

Abstract: Glioblastoma (GBM) is the most aggressive primary brain tumor and remains refractory to current therapies. Recent studies have revealed that glioma progression is strongly influenced by interactions with surrounding neural and immune cells, suggesting that cell-cell communication within the tumor microenvironment plays a central role in disease progression. However, the nanoscale organization of these interactions remains poorly understood due to the limited spatial resolution of conventional imaging approaches. To address this challenge, we are developing a Nano Expansion Microscopy (NanoExM)-based imaging platform to investigate cellular communication networks within the GBM microenvironment. NanoExM enables nanoscale visualization of cellular membranes, protein biomarkers, and molecular architectures while preserving tissue context, providing a unique opportunity to examine spatial relationships among tumor cells and neighboring cell populations. Using mouse models of glioblastoma, we

combine tissue expansion, multiplexed fluorescence labeling, and high-resolution imaging to map the spatial organization of glioma cells, immune cells, and neural elements within the tumor microenvironment. Emphasis is placed on identifying cellular interfaces and microenvironmental niches that may support tumor progression and local remodeling of brain tissue. This work establishes a framework for investigating cell-cell communication in GBM at nanometer-scale resolution and provides new insights into the spatial biology of tumor-host interactions in the brain. More broadly, the approach may facilitate the study of complex cellular communication networks across neurological diseases.

Disclosures: S. Lee: None. **J. Kang:** None.

Poster

PSTR217: Neuro-Oncology: Tumor Microenvironment and Immune Signaling

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR217.20/T5

Topic: B.10. Neuro-Oncology

Support: NIH-R16
INBRE

Title: Ceramide Mimetics Drive Neuronal Differentiation and Immunogenic Cell Death in Neuroblastoma

Authors: *S. MATEEN[1], S. PASHIKANTI[2];
[1]Idaho State Univ., Pocatello, ID; [2]Idaho State Univ., POCATELLO, ID

Abstract: Neuroblastoma is the most common extracranial solid tumor of childhood and remains a leading cause of cancer-related mortality in pediatric patients. Despite advances in multimodal therapy, high-risk neuroblastoma frequently develops resistance and relapses, highlighting the need for novel therapeutic approaches. Sphingolipid metabolism plays a central role in regulating tumor cell survival, differentiation, apoptosis, and immune responses through the dynamic balance between pro-apoptotic ceramide and pro-survival sphingosine-1-phosphate (S1P), collectively known as the ceramide/S1P rheostat. Recent studies have demonstrated that modulation of this pathway can promote immunogenic cell death (ICD) and enhance antitumor immunity.To exploit this therapeutic vulnerability, we employed a chiral pool medicinal chemistry strategy to synthesize a focused library of ceramide mimics inspired by bioactive sphingolipids. Compounds were evaluated in neuronal cancer models through the NCI-60 Human Tumor Cell Line Screen, and structure–activity relationship analyses were performed to identify molecular features associated with anticancer activity. Several analogs exhibited low-micromolar growth inhibitory activity in neuroblastoma cell lines. Pharmacophore mapping revealed a conserved sphingoid amino alcohol motif associated with enhanced potency. Active compounds induced morphological changes consistent with neuronal differentiation and promoted apoptotic cell death. Preliminary mechanistic studies suggest that these effects are

mediated through modulation of sphingolipid signaling pathways and activation of ICD-associated responses.These findings support the ceramide/S1P rheostat as a promising therapeutic target in neuroblastoma and identify novel ceramide mimics as potential modulators of tumor differentiation and immune activation. This work establishes a foundation for the development of sphingolipid-based therapeutics and combination immunotherapy strategies for the treatment of aggressive neuronal malignancies.

Disclosures: S. Mateen: None. **S. Pashikanti:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.01/T6

Topic: C.01. Brain Wellness and Aging

Support: R01MH133561
R01AG080790
R01AG076949

Title: Neurogenesis and gliogenesis in the normal ageing hippocampus: single-cell resolution spatial transcriptomic signature

Authors: *X. HUANG[1], L. POLIZZI[2], R. RAMKUMAR[3], V. ARANGO[5], R. HEN[6], M. BOLDRINI[4];
[1]New York State Psychiatric Inst., Harrison, NJ; [2]Univ. of Trento and Columbia Univ., Trento, Italy; [4]Psychiatry, [3]Columbia Univ., New York, NY; [5]NIMH, NIH, Natl. Inst. of Mental Hlth., SHRUB OAK, NY; [6]Columbia University, New York State Psychiatric Inst., New York, NY

Abstract: Population aging presents a major and growing health challenge. Our previous studies suggest that hippocampal neurogenesis may persist during healthy human aging, whereas angiogenesis and neuroplasticity decline in older individuals. However, gliogenesis remains relatively understudied, and how these processes vary across age groups and hippocampal cell types remains unclear. In aging mice, there is a propensity for neural progenitors to favor the glial fate *versus* the neuronal fate.To characterize neurogenic and gliogenic cell lineages in the normal aging human hippocampus, we applied single nucleus RNA and ATAC sequencing (snMultiome-seq) to 46 hippocampal samples from 20 donors across young, middle-aged, and older adult groups (ages 27-74 years), 20% females, and Xenium spatial transcriptomic to four hippocampus sections, two using the 266-gene panel (age = 31, 59) and two suing the 5,000-gene panel (age = 28, 37; 10x Genomics).Single-nucleus RNA-seq profiles were analyzed to define major hippocampal cell types (harmony integration was applied to correct for sample-, batch-, and sex-associated effects), identify neurogenic and gliogenic lineage cells (Fig 1A), and compare their transcriptional profiles between younger and older subjects. Age-group composition analysis showed that NB (neuroblasts), GC.2, and GC.3 (granule cell subtypes)

were primarily contributed by the young and middle-aged groups. Meanwhile, the proportions of NSC.1 and NSC.2 (neural stem cell subtypes), astro-like NSC (astrocyte-like neural stem cells), InP (intermediate progenitors), and NB progressively decreased with aging (Fig 1B). Xenium was used for validating cell cluster and gene expression distribution in the anatomical context (Fig 1C).Together, these findings provide a single-cell and spatial framework for understanding age-associated neurogenic and gliogenic programs that support hippocampal maintenance during normal aging.

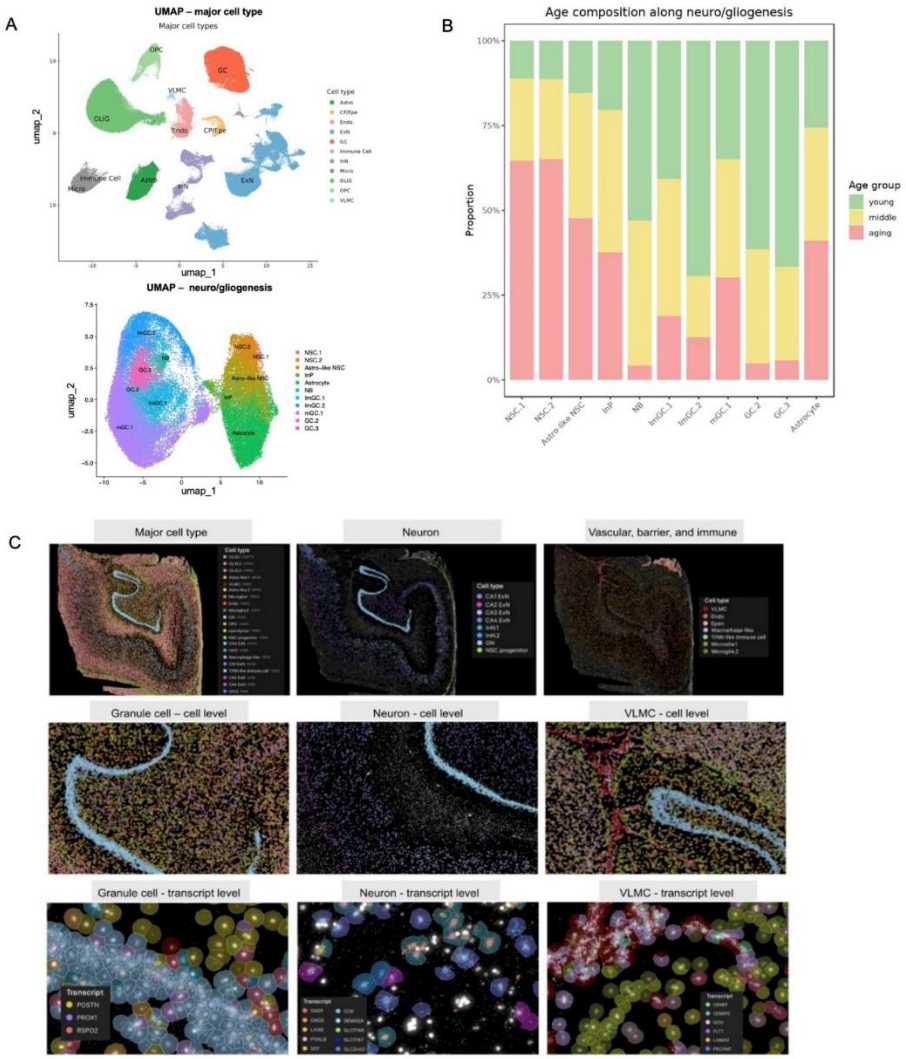


Figure 1 Integrated single-cell and spatial profiling of the human hippocampus
(A) Major hippocampal cell types and neurogenesis/gliogenesis lineage annotations shown on UMAP
(B) Age-group proportions of neurogenesis/gliogenesis-associated subtype
(C) Xenium spatial transcriptomics captures the spatial distribution of these cell states across

Disclosures: X. Huang: None. **L. Polizzi:** None. **R. Ramkumar:** None. **V. Arango:** None. **R. Hen:** None. **M. Boldrini:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.02/T7

Topic: C.01. Brain Wellness and Aging

Support: R01AG067781
U19AG073153
P30AG072977

Title: Greater integrity of neuronal dendritic tree in the anterior cingulate cortex of cognitive SuperAgers

Authors: E. ADEBANJO[1], I. A. AYALA[2], M. MATHER[4], R. J. CASTELLANI[5], P. JAMSHIDI[6], T. GEFEN[7], M.-M. MESULAM[3], *C. GEULA[8];
[1]Northwestern Sch. of Feinberg of Med., Chicago, IL; [3]Norrthwestern Univ., [2]Northwestern Univ., Chicago, IL; [5]Pathology, [4]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [6]Northwestern University, Feinberg Sch. of Med., Chicago, IL; [7]Cognitive Neurol. and Alzheimer's Dis. Ctr., Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL; [8]Northwestern Univ. Med. Sch., Chicago, IL

Abstract: Cognitive SuperAgers are individuals over age 80 whose performance on tests of episodic memory are equal to or better than individuals 20-30 years younger. Previously we demonstrated that SuperAgers exhibit preserved cortical thickness compared to age-matched cognitively average peers and demonstrate thicker anterior cingulate cortices (ACC) when compared with middle-aged individuals. Reduced cortical neuronal dendritic extent is a consistent feature of normal aging. The purpose of this study was to determine whether greater integrity of the dendritic tree may contribute to the increased thickness of the ACC in SuperAgers. Blocks of fresh-frozen tissue from the ACC were obtained from the Northwestern University ADRC Brain Bank. The cohort consisted of 5 SuperAgers and six control participants ranging from cognitively average to mildly impaired prior to death. The Golgi-Cox method was used to selectively impregnate individual neurons and their processes. Tissue blocks were immersed in Golgi-Cox solution for three weeks, with change to fresh solution after 12 hours. Blocks were taken through sucrose gradients (30-60%) and sectioned at 100 µm, mounted on slides and allowed to dry for 5-6 days. Slides were then immersed in a solution of 2/3 ammonium hydroxide to develop the reaction product and visualize neurons. The Neurolucida software was used to reconstruct and quantify dendritic architecture in approximately 30 neurons per participant. Scholl's concentric circles analysis was performed to determine measures of dendritic complexity in 10 µm increments away from the cell body. Overall, dendrites extended up to 170 µm from the cell body. Nearly all numeric measures of dendritic extent were higher in SuperAgers compared to controls. On average dendritic surface area and volume were significantly higher in SuperAgers ($p<0.04$), with higher dendritic length approaching significance ($p<0.07$). Density of dendrites was significantly higher in SuperAgers at 40 µm from the cell body ($p<0.04$). The length of dendrites between concentric circles 40-60 µm from the cell body was significantly higher in SuperAgers ($p<0.003$), as were surface area ($p<0.004$),

and volume ($p<0.0001$) at 20-40 µm. The dendritic tree of neurons extended beyond 150 µm from the cell body in 3 SuperAgers but only in 1 control participant. These preliminary findings suggest greater integrity of neuronal dendritic tree in SuperAgers, and in combination with our previous findings, point to enhanced neurosynaptic health in SuperAgers. Greater integrity of neuronal dendritic tree in the ACC may contribute, in part, to the higher thickness of this region in SuperAgers.

Disclosures: E. Adebanjo: None. **I.A. Ayala:** None. **M. Mather:** None. **R.J. Castellani:** None. **P. Jamshidi:** None. **T. Gefen:** None. **M. Mesulam:** None. **C. Geula:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.03/T8

Topic: C.01. Brain Wellness and Aging

Support: IMSS Grant 2023-785-027

Title: Associations Between Circulating Inflammatory Cytokines and Intrinsic Capacity Domains in Older Mexican Adults

Authors: *P. GARCIA-DELATORRE[1], N. A. RIVERO-SEGURA[2], J. GOMEZ-VERJAN[3]; [1]Unidad de Investigacion Epidemiologica y en Servicios de Salud, Area Envejecimiento, Inst. Mexicano del Seguro Social, Mexico City, Mexico; [2]Direccion de Investigacion, Inst. Nacional De Geriatría, Mexico City, Mexico; [3]Res. Dictatoriate, Natl. Inst. of Geriatrics (INGER), Mexico City, Mexico

Abstract: INTRODUCTION: Given the rapid growth of the global population, healthy aging has emerged as a public health priority, prompting the World Health Organization to propose a key indicator for it: intrinsic capacity (IC). IC is defined as the sum of a person's physical and mental abilities that determines their functional capacity in interacting with the environment. This concept encompasses five domains: mobility, vitality, cognition, psychological, and sensory function. One of the biological mechanisms proposed to contribute to functional decline in older adults is low-grade chronic inflammation associated with aging, known as inflammaging. Various cytokines and chemokines are involved in processes associated with frailty, sarcopenia, cognitive decline, and chronic diseases; however, the association between specific inflammatory markers and the domains of intrinsic capacity has not been thoroughly studied. METHODS: A cross-sectional study was conducted as part of the Cohort Study on Obesity, Sarcopenia, and Frailty in Older Mexican Adults (COSFAMM). Sociodemographic, clinical, and anthropometric data were collected from 400 older adults who agreed to participate in this project and signed an informed consent form. A composite score for intrinsic capacity was calculated using previously validated cutoff points. Serum cytokine concentrations were quantified using multiplex technology (Bio-Plex 17-plex panel). Deviations from reference ranges were estimated, and the

association between inflammatory biomarkers and domains of intrinsic capacity was explored using Spearman's correlations. RESULTS: A mean age of 67.8 ± 7.1 years; 55.8% were women. The mean body mass index was 28.4 ± 5 kg/m², and 40.2% were on multiple medications. The mean IC score was 6.46 ± 1.33. Most participants were classified as declining IC (86.9%), 9.3% as loss of IC, and only 3.8% as high or stable IC. The domains most frequently impaired were mobility (85.4%), sensory function (81.2%), and cognition (71.6%), followed by psychological function (59.3%) and vitality (20.6%). The cytokines with the highest prevalence of elevated levels were IL-17 (94.5%) and MIP-1β (66.6%), followed by IL-7 (12.6%) and G-CSF (12.3%). Correlation analysis revealed significant associations between IL-4 and the locomotion domain, and between IL-7 and IL-10 and the cognitive domain. MIP-1β was associated with sensory function. CONCLUSIONS: Inflammation is associated with certain domains of intrinsic capacity but does not account for intrinsic capacity in this specific cohort.

Disclosures: P. Garcia-delaTorre: None. **N.A. Rivero-Segura:** None. **J. Gomez-Verjan:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.04/T9

Topic: C.01. Brain Wellness and Aging

Support: CIHR

Title: Paired Neuroimaging and Transcriptomics in the Same Individuals Reveal Region-Specific Molecular Correlates of Brain Structure

Authors: *T. DELONG[1,3], X. ZHOU[1,3], C. GAITERI[5], B. NG[5], P. ZHUKOVSKY[2], S. TRIPATHY[2,4];
[2]Dept. of Psychiatry, [1]Univ. of Toronto, Toronto, ON, Canada; [3]Krembil Ctr. for Neuroinformatics, Ctr. for Addictions and Mental Hlth., Toronto, ON, Canada; [4]Krembil Ctr. for Neuroinformatics, Ctr. for Addictions and Mental Hlth., Toronto, ON; [5]Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL

Abstract: Previous imaging-transcriptomics studies have linked brain structure to gene expression using unpaired data or RNA from a single brain region. Datasets with paired structural magnetic resonance imaging (MRI) and ribonucleic acid (RNA) data from multiple regions per subject enable direct analysis of how transcriptomic variation across individuals relates to their brain structure.
We performed association analysis on individuals with ante-mortem MRI and post-mortem bulk RNA sequencing (RNAseq) from five brain regions - the dorsolateral prefrontal cortex (n = 122), the temporal cortex (n = 99), the frontal cortex (n = 97), the posterior cingulate cortex (n = 110), and the head of the caudate nucleus (n = 50). 128 total individuals were examined in this study.

92 of them are women and 36 are men. 64 are cognitively healthy controls, 25 have mild cognitive impairment, and 39 were diagnosed with Alzheimer's Disease based on clinical examination ante-mortem and brain tissue pathology post-mortem. On average, the study participants were 91.5 ± 5.97 years of age at death.
Regional cortical thickness, surface area, volume, and curvature were estimated using FreeSurfer. We applied linear models to assess cross-sectional gene-MRI associations.
We identified 6897 genes demonstrating significant associations with MRI structural features across the five examined regions (pFDR < 0.1). Imaging-transcriptomic associations were region-specific, with minimal overlap across brain regions. Comparing temporal cortex RNA to middle temporal cortical volume yielded 1873 significant genes, 1504 of them not present in gene sets for the other features and sample sites. Cell type marker enrichment analysis suggests that inter-region differences in cell type composition and activity drive associations between gene expression and brain structure. For example, greater temporal cortex volume was associated with increased excitatory neuron expression (p=1.9e-5) and decreased microglia (p=2.6e-7) in the temporal cortex.
Our findings help bridge the gap between macro-scale brain imaging and micro-scale omics. By linking MRI features to underlying molecular mechanisms, we can more accurately identify and interpret neuroimaging biomarkers in psychiatric disorders and aging.

Disclosures: T. DeLong: None. **X. Zhou:** None. **C. Gaiteri:** None. **B. Ng:** None. **P. Zhukovsky:** None. **S. Tripathy:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.05/T10

Topic: C.01. Brain Wellness and Aging

Support: MEXT/JSPS KAKENHI Grant Number 22K15660
Grant Number JPJ013268 from the Acquisition, Technology & Logistics Agency (ATLA)

Title: Modeling Pharmacologically Induced Cellular Senescence in Microglia-Containing Human Cortical Organoids

Authors: *H. ODAKA[1], Y. KUSAKA[2], H. SHIMA[3];
[1]Cell. and Mol. Biotech. Res. Inst., [2]Sensing Technol. Res. Inst., [3]Core Electronics Technol. Res. Inst., Natl. Inst. of Advanced Industrial Sci. and Technol., Tsukuba, Ibaraki, Japan

Abstract: Age-related declines in brain function and the development of neurodegenerative diseases are closely associated with cellular senescence and chronic inflammatory responses. In particular, microglia in the aging brain are thought to acquire a pro-inflammatory phenotype, thereby affecting neural stem cell niches and neuronal plasticity. However, in vitro models that

recapitulate aging-associated phenotypes of the human brain remain limited.In this study, we investigated whether key aging-associated phenotypes could be reproduced in human induced pluripotent stem cell-derived cortical organoids containing microglia through pharmacological induction of cellular senescence. After senescence induction, changes in the expression of genes related to cellular senescence, inflammation, and microglial activation were analyzed. Immunohistochemical analyses were also performed to evaluate alterations in microglial distribution and abundance. To assess the impact of senescence induction on the neural stem/progenitor cell pool, the expression of neural stem cell markers was examined. This study assesses the utility of microglia-containing cortical organoids as a pharmacologically induced cellular senescence model and explores their potential application in studies of aging-related cognitive impairment.

Disclosures: H. Odaka: None. **Y. Kusaka:** None. **H. Shima:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.06/T11

Topic: C.01. Brain Wellness and Aging

Support: 2RF1NS106721- 06A1 NINDS
5R01AG072489 -05 NIA
Glenn and AFAR foundation postdoctoral fellowship

Title: Investigating Microglial Plasticity and Function in Brain Aging

Authors: *V. SAHASRABUDDHE[1], D. RIBEIRO[3], E. HAYS[4], P. HWANG[2], A. SCHAEFER[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY, ; [3]Mount Sinai Sch. of Med., New York, NY, ; [4]New York, NY.

Abstract: Aging is the highest risk factor for cognitive decline and neurodegeneration. Yet, the mechanisms underlying brain aging and the extent to which it is driven systemically or by dysfunction of specific cell populations—remain elusive. Among brain cell types, microglia—the brain's resident macrophages—exhibit some of the earliest age-related changes, including impaired neuro-supportive functions and heightened inflammation. However, it remains unclear whether these changes are intrinsic drivers of brain aging or secondary responses to the aging milieu. It is also unknown whether such alterations are stable and potentially irreversible or instead plastic and maintained by ongoing exposure to the aged brain environment.To address these questions, I am employing a microglial transplantation paradigm. By transplanting microglia across age groups, I aim evaluate (a) how donor age and host environment influence microglial phenotypes to define the limits of microglial plasticity, and (b) how these interactions affect molecular and cellular indices of brain function. This work will provide mechanistic

insight into how microglial aging shapes neural health, informing strategies for brain rejuvenation and the prevention of age-related neurodegenerative disease.

Disclosures: V. Sahasrabuddhe: None. **A. Schaefer:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.07/T12

Topic: C.01. Brain Wellness and Aging

Support: R01AG067025
R01AG082185
R01AG065582
Human tissues were obtained from the NIH NeuroBioBank at the Mount Sinai Brain Bank (MSSM; supported by NIMH-75N95019C00049), and NIMH-IRP Human Brain Collection Core (HBCC, project # ZIC MH002903)
Intramural Research Program of the National Institutes of Health (NIH)
R01MH106460
R01MH111601
Wood Next Foundation

Title: Age-Related Differences in Cell Type-Specific Gene Expression Rhythms in Human DLPFC

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Abstract: Changes in circadian rhythms are a notable feature of both healthy and pathological aging. At the molecular level, gene expression rhythms have been shown to drastically change with age, suggesting that this may be an important feature of late adulthood. However, these studies have primarily been done using bulk tissue RNA-sequencing, which does not measure which cells RNA is from. Notably, the prefrontal cortex is made up of many different cell types, which all play different functional roles, and the role of molecular rhythms within these cells is not well understood. As such, we used single nucleus RNA-sequencing (snRNA-seq) data from Dorsolateral Prefrontal Cortex tissue of 192 human subjects with no diagnosed psychiatric illness or neurodegenerative disease, and for whom we could identify their time of death (TOD). We then used a joint rhythmicity analysis to determine and compare 24 h gene expression rhythms in Adulthood (21 - 60 years old (yo); n = 116) and Late adulthood (> 61 yo; n = 76) age groups within 26 cell type subclasses. Overall, our findings suggest that an intact, rhythmic molecular clock, which is known to be important for regulating sleep-wake patterns, cognitive function, and cellular metabolism, is a fundamental component of the DLPFC transcriptomic landscape during

adulthood, particularly in neuronal subclasses. However, in late adulthood, rhythmicity of these core circadian clock genes is lost, but different genes gain a 24 h rhythmic expression pattern, consistent with a growing literature that has observed circadian reprogramming within various tissue types and across different species (humans, mice, Drosophila). Microglia and oligodendrocytes in particular had more rhythmic genes in late adulthood. These were enriched for genes associated with the unfolded protein response, which suggests increased demand for proteins that regulate quality control of protein synthesis during aging, perhaps in response to higher activity and/or cellular stress within these cells. Investigating how these patterns influence neuropsychiatric and neurodegenerative processes may offer novel strategies for mitigating both age-related and disease-associated cognitive decline and improving overall brain health.

Disclosures: M.R. Scott: None. **H. Yang:** None. **T. Clarence:** None. **D. Lee:** None. **P. Roussos:** None. **C.A. McClung:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.08/T13

Topic: C.01. Brain Wellness and Aging

Support: NIH grant R01AG067025
NIH grant R01AG082185
NIH grant R01AG065582
NIH grant R01MH125246
NIH grant R01AG050986
NIH grant R01AG095776
NIH grant U24AG087563
Novo Nordisk Foundation NNF14CC0001
Novo Nordisk Foundation NNF20SA0035590
Veterans Affairs Merit grant BX004189

Title: Lifespan single-cell transcriptomic atlas of the human prefrontal cortex

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Abstract: The human brain undergoes profound changes from early development through late adulthood, shaping cognition, behavior, and vulnerability to disease. Understanding how these changes are organized within specific brain regions and cell types is essential for interpreting normal aging and its relationship to psychiatric and neurodegenerative disorders. The dorsolateral prefrontal cortex plays a central role in higher cognitive functions and is particularly sensitive to age-related decline, yet its cellular and molecular programs across the human lifespan remain poorly defined. Most existing studies have focused on restricted age ranges or disease-affected brains, limiting the ability to distinguish normative developmental and aging trajectories from pathological processes. Consequently, a comprehensive, lifespan-resolved reference of cellular states in the human prefrontal cortex has been lacking. Using a single-nucleus transcriptomic atlas spanning the human lifespan, we show that the dorsolateral prefrontal cortex exhibits non-linear, cell-type-specific transcriptional trajectories, characterized by dynamic remodeling during development, relative stability in midlife, and selective molecular reactivation in late adulthood. We identify distinct neuronal and glial programs, including early-life neuronal resilience pathways and late-life glial programs associated with immune activation, stress responses, and circadian reorganization. These programs are anatomically organized across cortical layers and gray-white matter domains, revealing coordinated spatial and molecular changes not previously appreciated. Together, these findings provide a framework for understanding how cellular programs transition from resilience to vulnerability in the human cortex and establish a foundation for interpreting age-related cognitive decline and disease risk.

Disclosures: H. Yang: None. **T. Clarence:** None. **M.R. Scott:** None. **S. Venkatesh:** None. **N.M. Tsankova:** None. **P.K. Auluck:** None. **S. Marenco:** None. **V. Haroutunian:** None. **G. Voloudakis:** None. **C.A. McClung:** None. **D. Lee:** None. **P. Roussos:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.10/T14

Topic: C.01. Brain Wellness and Aging

Support: 1R01NS148641-01
1R56NS138538-01

Title: Mechanistic dissection and therapeutic targeting of a maladaptive DNA damage response in Alzheimer's disease

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Abstract: Aging remains the leading risk factor for idiopathic Alzheimer's disease (AD). Despite strong epidemiological associations, a key causal question remains: how do specific age-related factors contribute to the development of AD and other neurodegenerative disorders (NDDs)? Recent human single-neuron sequencing studies confirmed the accumulation of non-germline inherited somatic mutations associated with aging and AD. Genomic instability stands as the foremost hallmark of aging . Our studies showed that overactive and persistent DNA damage response (DDR) is a prominent feature in Aging, Parkinson's disease (PD), Huntington’s disease (HD), in animal models and patients of AD . We observed extensive maladaptive DDR in 3XTg AD mouse models that can drive cellular senescence, chronic neuroinflammation, autophagy-lysosome dysfunction and contribute to AD pathology. Extensive DDR in 3XTg AD mouse models disrupted contextual fear conditioning memory engram in 3XTg AD mouse model. We leveraged the Agora research cohort to defined and evaluated the contribution of maladaptive DNA damage response (DDR) genes (ATM, CHEK2, TP53, PARP1, CDKN1A, CDKN2A, and RELA) to AD risk (maladaptive DDR). We observed significantly upregulated expression of the maladaptive DDR gene set across nine brain regions , with the most significant and consistent across all maladaptive DDR gene in the parahippocampal gyrus (PHG), superior temporal gyrus (STG), and temporal cortex (TCX) . Notably, these regions correspond to primary sites of AD-related pathological vulnerability. ATM, a central orchestrator of DDR, is consistently upregulated in vulnerable AD brain regions and has a prominent peak at an AD Target Risk Score of 3.63, indicating a significant positive association with AD risk. We analyzed the human hippocampus RNA-seq dataset GSE173955 and revealed the maladaptive DDR gene set shows significant positive enrichment exceeding canonical Reactome/KEGG DDR pathways in human AD hippocampus. In 3xTg-AD mouse model, both pharmacological inhibition of DDR via a highly brain-penetrant ATM inhibitor, AZD-1390 and a Seek-and-Rescue genetic strategy to transient knockdown of Atm in neurons with maladaptive DDR can improve cognitive deficits, DDR activation, amyloid-β (Aβ) burden, phosphorylated tau pathology, and neuroinflammation in 3xTg-AD mice at 12 months of age. Our study unravels the causal pathogenic role of a maladaptive DDR in AD and holds potential of targeting maladaptive DDR as a disease-modifying strategy to a wide range of CNS disorders associated with genomic instability.

Disclosures: F. Huang: None. **C. Haacker:** None. **W. Chen:** None. **J. Li:** None. **X. Tian:** None. **X. Lu:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.11/T15

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIDA DP1 DA056018

Title: Single-molecule profiling of mitochondrial DNA accessibility in human and mouse brain

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Abstract: Mitochondria are central regulators of cellular metabolism and are particularly important in the brain, where neurons and synapses have high energetic demands. Mitochondrial DNA (mtDNA) encodes essential components of the oxidative phosphorylation system, and its transcription, replication, and maintenance are closely linked to mitochondrial function. Mammalian mtDNA is a circular genome of approximately 16 kb packaged into nucleoids, whose organization may represent an important layer of mitochondrial genome regulation. However, mtDNA accessibility and compaction remain difficult to measure at single-molecule resolution in brain-derived mitochondrial populations. Here, we applied Fiber-seq, a Hia5 adenine methyltransferase-based long-read single-molecule accessibility mapping method, to profile mtDNA accessibility in human and mouse brain-derived samples. To generate mtDNA-enriched libraries, we used differential centrifugation and Percoll gradient isolation to prepare bulk brain mitochondria as well as synaptic and non-synaptic mitochondrial fractions, followed by Fiber-seq library preparation. To adapt accessibility calling to mouse brain mtDNA, we optimized Hia5 enzyme concentration and trained a sequence-context-aware hidden Markov model using mouse mtDNA libraries and Hia5-treated LRPCR-derived mtDNA controls. In pilot human brain Fiber-seq data from 34 samples, with an average of approximately 600 mitochondrial reads per sample, mitochondrial reads recapitulated key features previously reported in a cell-based mtDNA Fiber-seq study, including a population of highly compacted mtDNA molecules with little or no detectable m6A labeling and a subset of molecules with accessible regions. Accessible molecules contained recurrent footprint-like protected segments overlapping mtDNA regulatory regions, including termination-associated sequence 2 and the heavy- and light-strand replication origin regions. In enriched mouse brain mtDNA libraries from three samples, we obtained 12,526-18,798 full-length mtDNA reads per sample and detected widespread mtDNA compaction and recurrent footprinting patterns. Together, these results establish a quantitative single-molecule workflow for investigating mtDNA compaction, accessibility, and footprint patterns in brain-derived mitochondrial samples. This approach provides a framework for ongoing comparisons of young and aged mouse cortex mitochondria and for profiling synaptic and non-synaptic mitochondrial fractions in human and mouse brain.

Disclosures: B. Jiang: None. **R. Watanabe:** None. **S. Akbarian:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.12/T16

Topic: C.01. Brain Wellness and Aging

Support: NIH IRTA

Title: Mitochondrial stabilization protects cholinergic axons from excitotoxic stress in aging

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Abstract: Aging in the brain is associated with mitochondrial dysfunction and impaired energy metabolism. Basal forebrain cholinergic neurons have long and extensively branched axonal arbors which require a healthy pool of mitochondria to keep up with the demand of millions of synapses across the cortical and subcortical space. We analyzed mitochondria morphology and distribution in cholinergic neurons across the lifespan in mice using the Chat-cre x mito-eGFP strain. In aged mice, we found that cholinergic axonal mitochondria were more vulnerable to stress than mitochondria found within their cell bodies. Aging altered the distribution of axonal mitochondria in the basolateral amygdala resulting in displacement from pre-synaptic release sites. In mice aged over 18 months, mitochondria damage is severe and appear as swollen aggregates engulfed by microglia. These mitochondrial changes appear to be an early indicator of degeneration and precede other markers of microtubule destabilization and retraction. Failure to clear mitochondria aggregates can disrupt the maintenance of ion gradients and compromises calcium buffering in axons. As energy failure and calcium dysregulation worsen, cholinergic axons become vulnerable to excitotoxic injury. To prevent this toxic aggregation, we used a pre-clinical drug known as IVO-21 to determine if mitochondrial stabilization could protect cholinergic axons from excitotoxic injury caused by repeat depolarization. We transfected cholinergic microexplants with channelrhodopsin to control neural firing and observed changes in axonal morphology and mitochondrial motility using a spinning disk confocal microscope. Consistent with our hypothesis, cholinergic axons subjected to repeat overstimulation exhibited cytoskeletal deformations, mitochondrial fission/fusion, and impaired axonal transport. However, with 24h pre-treatment of IVO-21, axons remained in-tact with no change in varicosities and maintained numbers of healthy mitochondria. These observations suggest that age-related mitochondrial impairment may lower the threshold for excitotoxic stress, promoting the progressive degeneration of cholinergic projections that contributes to cognitive decline and that treatment with the mitochondrial drug IVO-21 supports mitochondrial function and axon resilience during prolonged periods of hyperactivity in-vitro.

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

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.13/T17

Topic: C.01. Brain Wellness and Aging

Support: R01 AG086136 (MJF) from NIH.

Title: Molecular markers of lumbar motor neuron death in ageing rats

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Abstract: Lumbar motor neurons (MNs) within the lateral motor column innervate the striated muscles of the lower limbs and are critical for the generation and control of locomotor behaviour. In both humans and Fischer 344 (F344) rats, age-related muscle weakness and motor dysfunction occur concomitantly with reductions in lumbar MN survival, implicating MN loss as a potent contributor to declining motor performance in old age. MN death in ageing follows the size principle, whereby larger, likely fast-fatigable MNs are preferentially lost. Several molecular markers have been associated with selectively vulnerable MN populations in mouse models of MN diseases, such as Amyotrophic Lateral Sclerosis (ALS). However, whether these markers identify vulnerable MNs during normal ageing remains unknown. We aimed to determine if matrix metallopeptidase-9 (MMP-9), a marker associated with vulnerable MN populations in ALS, was expressed predominantly in larger MNs in young rats, and whether this expression is reduced or absent in old rats. We used immunofluorescence and confocal microscopy to evaluate MMP-9 expression within MNs in young (6-month) and old (24-month) female and male F344 rats (n=10 per age per experiment, 50 MNs counted within each rat). In young rats, there was a significant increase in MMP-9 expression within larger MNs compared with smaller MNs. By contrast, in old rats, remaining larger MNs no longer exhibited elevated MMP-9 expression. These findings are consistent with MMP-9 serving as a molecular maker of larger Fast Fatigueable type lumbar MNs. Although more work is needed to determine if MMP-9 expression reflects selective death of MMP-9 expressing MNs or downregulation of MMP-9 within surviving MNs, our results identify MMP-9 as a potential molecular marker of selectively vulnerable MN populations during ageing.

Disclosures: S. Cheung: None. **M.J. Fogarty:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.14/T18

Topic: C.01. Brain Wellness and Aging

Support: Department of Defense HT94252310972

Title: Fisetin treatment improves cognitive function with alleviation of cellular senescence and Neuroinflammation in a rat model of chronic Gulf War illness

Authors: *P. TARALE[1], S. ATTALURI[1], Y. SOMAYAJI[1], L. N. MADHU[1], B. SHUAI[1], M. KODALI[1], C. HUARD[1], S. JIMENEZ[1], S. PANNURI[1], C. FAN[1], K. SULLIVAN[2], A. K. SHETTY[1];
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Abstract: Gulf War illness (GWI) is a multi-symptom disorder affecting ~30% of veterans from the first Gulf War. Affected individuals exhibit impaired brain function, including accelerated aging and cognitive and mood dysfunction. Exposures to GWI-related (GWI-R) chemicals and stress during deployment are considered major contributing factors in GWI pathogenesis. This study evaluated the efficacy of fisetin, a natural compound known to reduce senescent cells and exert anti-inflammatory effects, in improving cognitive and mood function. Two-month-old male Sprague Dawley (SD) rats (Envigo) were exposed to GWI-R chemicals such as pyridostigmine bromide (PB, 2 mg/kg), permethrin (PER, 0.2 mg/kg), and N,N-diethyl-meta-toluamide (DEET, 60 mg/kg), and subjected to 15 minutes of restraint stress daily for 28 consecutive days. Treatment with vehicle (GWI-VEH) or fisetin (20 or 40 mg/kg, orally, 5 days/week; GWI-FIS20 and GWI-FIS40 groups) began 13 months post-exposure and continued for 3.5 months, until euthanasia at 18.5 months of age. Between 16 and 18 months of age, animals underwent cognitive and mood function assessments. The GWI-VEH group demonstrated impairments in object-location and associative recognition memory tasks and displayed anhedonia compared to naïve controls. In contrast, the GWI-FIS20 and GWI-FIS40 groups showed improved cognitive performance and no anhedonia. Analysis of hippocampal tissues at 18.5 months revealed increased expression of senescence-related genes, including *CDKN1a* and *GLB-1*, as well as genes associated with the senescence-associated secretory phenotype, such as *MCP1, IL6, IL1a, VEGFa*, and *TNF*, in the GWI-Veh group. Fisetin treatment reduced the expression of genes *CDKN1a, MCP1, IL1a, IL6,* and *VEGFa* in GWI rats to levels seen in naïve rats. The hippocampal neurons in the GWI-Veh group also exhibited higher area fractions of p16 and p21 immunoreactivity compared to the naïve group, reflecting increased senescence markers. These markers were decreased in GWI groups treated with fisetin. Fisetin treatment also reduced the proportion of microglia expressing the NLRP3 inflammasome complex and the area fraction of GFAP-positive astrocyte elements, compared to rats in the GWI-Veh group. These findings suggest that fisetin treatment can attenuate accelerated neuronal senescence and microglia- and astrocyte-mediated neuroinflammation in the hippocampus of GWI rats. Therefore, long-term fisetin supplementation may represent a promising strategy to improve cognitive function by reducing neuroinflammation in individuals with GWI.

Disclosures: P. Tarale: None. **S. Attaluri:** None. **Y. Somayaji:** None. **L.N. Madhu:** None. **B. Shuai:** None. **M. Kodali:** None. **C. Huard:** None. **S. Jimenez:** None. **S. Pannuri:** None. **C. Fan:** None. **K. Sullivan:** None. **A.K. Shetty:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.15/T19

Topic: C.01. Brain Wellness and Aging

Support: U01-MH121260
R01-AG060931
R00-AG051764

R00-AG075241
R01-HG010632
R01-MH118203
R01-MH096875
R37-MH109728
R21-AG073958
R01-MH108627
R56-AG071023
T32-AG000057
T32-AG044402
T32-AG082658
P40-OD012217

Title: Single-nucleus profiling reveals age-associated transposable element expression across the rhesus macaque brain

Authors: *K. WATKINS[1], W. YANG[4,6], K. E. LEINENWEBER[2], A. DECASIEN[7], M. O'NEILL[8], M. O. BOHLEN[9], A. MELIN[10], J. HIGHAM[11], M. J. MONTAGUE[12], M. L. PLATT[13], K. CHIOU[14], J. SHENDURE[5], N. SNYDER-MACKLER[3];
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Abstract: Aging is accompanied by a progressive loss of molecular fidelity and regulatory control across multiple levels of genome function. One consequence of this dysregulation is the increased expression of transposable elements (TEs), repetitive genomic sequences that are normally silenced but become more active with age. Because TE activation can compromise genomic stability and lead to inflammation, it has emerged as a potential contributor to age-related brain dysfunction and neurodegenerative disease. However, most evidence for age-associated TE activity comes from bulk tissue studies, limiting insight into cell-type-specific patterns. Here, we leveraged a large-scale single-nucleus RNA-sequencing dataset from rhesus macaques, an established model for human brain aging. We used 5.3 million snRNAseq transcriptomes from 582 samples (11 regions; 55 animals; aged 0.4 to 21yr), which we resolved to 225 subtypes. Overall, TE expression (as a fraction of total transcripts) was significantly higher in older individuals in every brain region except the midbrain, where we observed lower TE expression in neurons and vascular cells (FDR < 0.05). We observed the biggest age-difference in TE expression in the hippocampus and entorhinal cortex regions (FDR < 0.05). Age-associated differences in TE expression were not uniform across TE classes, with the strongest signal observed in transcripts from short interspersed nuclear elements (SINEs) (FDR < 0.05). We next tested for cell subtype- and region-specific age effects on TE expression and found that 20% of TEs are differentially expressed with age in at least one context (FDR < 0.05), including 80% of tested DNA TEs, 21% of LINEs, 16% of SINEs, and 15% of LTRs. Age-associated differences in TE expression were most pronounced in both homeostatic and

inflammatory microglial subtypes (mean β_{age}=0.07, FDR < 0.05). We also identified higher expression of TEs in an ALS-associated oligodendrocyte subtype in the entorhinal cortex and thalamus of older animals (mean β_{age}=0.08, FDR < 0.05). The largest numbers of individual age-differentially expressed TEs (aDE-TEs) were detected in astrocytes, which accounted for 28% of all aDE-TEs, and in the cerebellum, which accounted for 34% (FDR < 0.05). Together, these findings reveal widespread, cell-type- and region-specific associations between age and TE expression in the primate brain. By characterizing TE expression dynamics at single-nucleus resolution, this work provides a framework for identifying cellular contexts in which TE activity may contribute to molecular vulnerability across the lifespan.

Disclosures: K. Watkins: None. **W. Yang:** None. **K.E. Leinenweber:** None. **A. DeCasien:** None. **M. O'Neill:** None. **M.O. Bohlen:** None. **A. Melin:** None. **J. Higham:** None. **M.J. Montague:** None. **M.L. Platt:** None. **K. Chiou:** None. **J. Shendure:** None. **N. Snyder-Mackler:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.16/T20

Topic: C.01. Brain Wellness and Aging

Support: FONDECYT 1231556 (JMC)
ANID 21240414 PhD Fellowship (IAT)

Title: Transglutaminases contribute to maintenance of mature brain organization and function in adult animals

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Abstract: Transglutaminases (TGs) are a family of enzymes characterized by their calcium-dependent transamidation activity. Although in higher mammals TG2 is the family member with the highest expression in the brain, TG2 KO mice show no major neurodevelopmental or behavioral phenotypes, which might be explained by compensation from other members of the TG family also expressed in mammalian CNS. We have proposed that simpler animal models are better suited to study the contribution of TGs to brain formation, maintenance and operation. In that regard, *Drosophila melanogaster* contains a single TG gene (dTG), but its contribution to brain development and function remains poorly understood. We have shown that whole-body mutations in dTG results in reduced locomotion and asocial-like behavior in flies, impairment in dopaminergic neuron development, and alters the brain transcriptome, phenotypes partially rescued by human TG6 expression. These observations point to developmental consequences of TG deficiency, but it remains unclear whether the resulting phenotypes depend on the timing of TG loss or reflect cell type-specific requirements. Here we show that during development, dTG

loss in neurons causes mild locomotor and neuronal morphological defects. In contrast, specific downregulation of dTG expression in neurons in adult flies reduces lifespan, induces ataxia-like age-dependent motor phenotypes, and promotes cluster-specific dopaminergic neurodegeneration. Interestingly, glial manipulations of dTG do not result in major alterations in any of the phenotypes studied. Our data support the contribution of neuronal TGs to the maintenance and operation of mature brain neurons and circuits.

Disclosures: I. Almonacid: None. **J. Almonacid:** None. **J.M. Campusano:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.17/T21

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01NS115876
NIH Grant R33AG076858
NIH Grant R56AG081262
NIH Common Fund
University of Maryland System, AIM-HI Challenge Award
MPower Early Scholars Investment Fund

Title: Lysosomal multi-omics reveals sphingolipid accumulations as driver of lysosomal dysfunction in the aging brain

Authors: *P. NGUYEN[1], C. SARKAR[3], Y. CHEN[4], M. WELDEMARIAM[5], A. MEHRABANI-TABARI[6], N. GORNY[7], O. PETTYJOHN-ROBIN[8], S. THAPA[9], M. KARBOWSKI[2], J. JONES[10], M. CUMMINGS[11], M. M. LIPINSKI[12];
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Abstract: Lipid metabolism is increasingly recognized as a key regulator of the aging process and changes in lipid homeostasis affect brain aging and its predisposition to neurodegenerative disease. During brain aging lipid changes have been specifically noted in lysosomes, but the identity of the accumulated lipids and their functional relevance have not been characterized. To address this gap, we performed a longitudinal analysis of enriched lysosomal fractions isolated from the mouse cortex, from the age of 3- to 24- months. Lysosomal fractions collected were subjected to integrated longitudinal mass spectrometry-based multi-omics, and machine learning

factor analyses. Our statistical and machine learning analyses identified two factors that demonstrate predictive power of age. Factor 1 was the strongest predictor, characterized by age-associated increases in multiple hexosylceramid (HexCer) species and their sulfonated derivative, sulfatides (SHexCer), as well as elevated myelin proteins, and protein associated with lysosomal storage diseases. Collectively, these results suggest age-dependent increase in lysosomal delivery of myelin component as the primary mechanism underlying aging pathology. To corroborate factor 1 predictions, we employed a combination of biochemical, imaging and flow cytometry approaches, which confirmed lysosomal accumulation of myelin components in both microglia and neuron, especially prominent in microglia. We proceeded to test the causation between myelin accumulation and lysosomal dysfunction *in vitro*. Following treatment of primary microglia cell with purified myelin, we observed that myelin phagocytosis resulted in significant reduction of lysosomal enzyme activity as measured by Cathepsin-D activity assay. Together with our in vivo finding, these results link myelin accumulation to age-associated alteration in lysosomal morphology, lysosomal dysfunction and inhibition of autophagy in both neurons and microglia. Our findings indicate that factors contributing to lysosomal aging resemble those observed in lysosomal storage diseases and underscore the significance of organelle-specific analyses for dissecting mechanisms contributing to brain aging**.**

Disclosures: P. Nguyen: None. **C. Sarkar:** None. **Y. Chen:** None. **M. Weldemariam:** None. **A. Mehrabani-Tabari:** None. **N. Gorny:** None. **O. Pettyjohn-Robin:** None. **S. Thapa:** None. **M. Karbowski:** None. **J. Jones:** None. **M. Cummings:** None. **M.M. Lipinski:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.18/T22

Topic: C.01. Brain Wellness and Aging

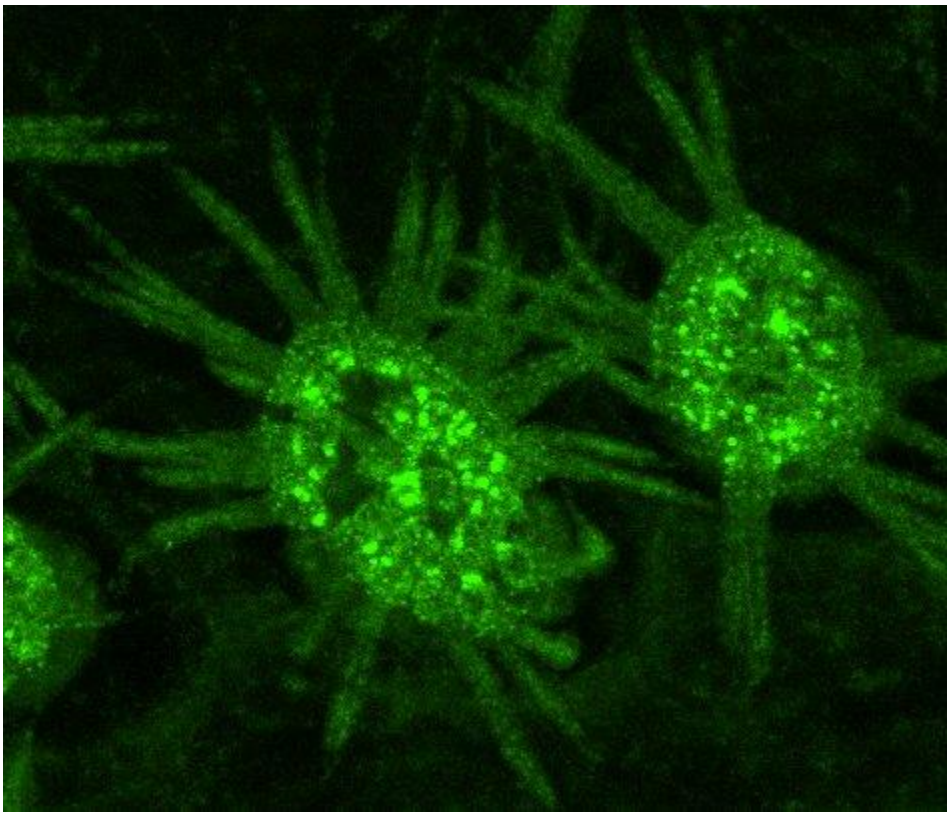
Support: Howard Hughes Medical Institute

Title: Age-related changes in olfactory sensory neuron cilia organization and ultrastructure

Authors: *C. M. OTT[1], W.-P. LI[2], M. R. TAVAKOLI[3], J. LIPPINCOTT-SCHWARTZ[3]; [1]HHMI Janelia Res. Campus, Ashburn, VA; [2]Electron Microscopy Shared Resource, Howard Hughes Med. Institute/Janelia Farm Res. Campus, Ashburn, VA; [3]Janelia Res. Campus, Ashburn, VA

Abstract: Olfactory function declines with age; however, in rodents, the number and length of olfactory cilia on sensory neurons varies little across lifespan. Multiple cilia project radially from the dendritic knob of olfactory sensory neurons (OSNs). Each ciliary microtubule axoneme is typically enveloped by the ciliary membrane, which anchors at the centriolar distal appendages. This architecture, along with the ciliary transition zone isolates the ciliary compartment creating a privileged and specialized signaling domain. Using total protein staining and the expansion

microscopy approach light microscopy-based connectomics (LICONN), cilia disorganization was observed in dendritic knobs of OSNs from a mouse older than 2 years. In addition, some cilia did not project directly into the extracellular space. Serial transmission electron microscopy of similarly aged mice revealed ultrastructural defects in many aged dendritic knobs that were only rarely seen in younger adult mice. In several cases, cilia were only partially enveloped by membrane, leaving portions of the ciliary axoneme exposed to the cytoplasm. These structural abnormalities may reduce the signaling capacity of olfactory cilia and thereby contribute to age-related declines in olfactory sensitivity.



Disclosures: C.M. Ott: None. **W. Li:** None. **M.R. Tavakoli:** None. **J. Lippincott-Schwartz:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.19/T23

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG093606
Macular Degeneration Foundation
Reeves Foundation

Title: MicroRNA signatures of early and advanced neurodegeneration in the aging human visual system

Authors: J. VU[1], *T. SHWANI[2,3], W. LIU[2], L. OWEN[4], I. KIM[5], M. DEANGELIS[1]; [1]Ophthalmology, [3]Neurosci. Program, [2]Univ. at Buffalo, Buffalo, NY; [4]Univ. of Cincinnati, Cincinnati, OH; [5]Harvard Med. Sch., Boston, MA

Abstract: Aging is associated with complex alterations in cellular regulation that progressively disrupt tissue homeostasis across organ systems. Across the aging central nervous system (CNS), neurodegenerative diseases are increasingly understood as disorders of disrupted gene regulation. The retina, a neuron-rich extension of the CNS, provides a unique window into these processes within the aging visual system and offers a tractable model for studying neurodegeneration. Age-related macular degeneration (AMD) is a progressive neurodegenerative disease and a leading cause of irreversible vision loss. In dry AMD, disease progression spans early and intermediate stages before advancing to geographic atrophy (GA), the late atrophic form defined by degradation of the macula, retinal pigment epithelium (RPE) loss, and secondary photoreceptor dysfunction. MicroRNAs (miRNAs) are key post-transcriptional regulators of gene expression and have been implicated in neuronal survival, inflammatory signaling, and stress-response pathways across neurodegenerative diseases. However, miRNA dysregulation in human AMD-affected tissue remains poorly characterized. To profile miRNA signatures across dry AMD, we processed macular RPE/choroid tissue from 60 rapidly recovered human donor eyes obtained within 6 hours postmortem. Donor eyes were rigorously phenotyped and classified as normal aged controls (n=30), intermediate AMD (iAMD; n=23), or GA (n=7). Across 855 profiled miRNAs, we identified significant stage-associated miRNA dysregulation. Compared with normal aging controls, 36 miRNAs were differentially expressed in iAMD and 88 miRNAs were differentially expressed in GA, while 11 miRNAs were differentially expressed between iAMD and GA. In contrast, 22 miRNAs were unique to iAMD and 74 miRNAs were unique to GA when each stage was compared with normal controls. Pathway analysis further revealed disease-stage-specific regulatory networks, supporting the idea that miRNA-mediated post-transcriptional control may contribute to the transition from aging to retinal degeneration. Together, these findings provide the first comprehensive miRNA profile of dry AMD in human macular RPE/choroid tissue and identify stage-specific regulatory signatures in the aging visual system. By positioning the eye as a tractable model of CNS aging, this work advances our understanding of miRNA dysregulation in retinal neurodegeneration and highlights candidate molecular pathways that may inform future biomarker and therapeutic development.

Disclosures: J. Vu: None. **T. Shwani:** None. **W. Liu:** None. **L. Owen:** None. **I. Kim:** None. **M. DeAngelis:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.20/T24

Topic: C.01. Brain Wellness and Aging

Support: R01 EY032519-01A1

Title: Depleting Optic Nerve Head Neural Progenitor Cells Increases Retinal Ganglion Cell Death in a Mouse Glaucoma Model

Authors: *J. JOUFFROY[1], S. BERNSTEIN[2];
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Abstract: Optic Nerve Head-Neural Progenitor Cells (ONH-NPCs) (Bernstein et al, 20206), present in the optic nerve head (ONH), contribute to maintaining normal optic nerve (ON) function and deplete with age (Bernstein et al, 2020). Rodent ONH-NPCs express the transcriptional factor Homeodomain only protein (Hopx). We developed a method to selectively deplete Hopx(+) ONH-NPCs in mice to determine effects of their depletion on retinal ganglion cells (RGCs) and the ON's response to stress. This approach utilizes expression of diphtheria toxin receptor (DTR) in Hopx(+)-NPCs. These NPCs are eliminated by diphtheria toxin (DT) administration via cerebral spinal fluid. This approach spares intraretinal Hopx(+) cells. By subsequently using a microbead glaucoma model, the role of NPCs to suppress RGC death during ON stress can be determined.
HOPX-Cre-ERT2 knockin was crossed with Rosa26 flox(DTR) to generate a double mutant mouse line that expresses DTR in Hopx(+) cells following tamoxifen administration. 4-hydroxytamoxifen was systemically administered six times over four weeks to enable DTR expression. Mice were then administered DT via an osmotic pump with an intracerebral cannula (Alzet kit #3) inserted in the lateral ventricle. This enabled continuous DT release into CSF for seven days. Mice were then injected with microbeads in the anterior segment of the left eye to raise intraocular pressure (IOP). Mice were perfused four weeks post-bead injection. Following fixation, eyes and ON's were cryoprotected and embedded in OCT. ONH tissue was cross-sectioned and reacted with primary antibodies to DTR and HOPX followed by fluorescent labeled secondary antibodies. Retinae were flat-mounted and reacted with primary antibodies to Brn3a (RGC nuclear marker). Tissues were viewed via confocal microscopy.
ONH-Hopx(+)/DTR(+) cells were successfully depleted following DT administration while sparing Hopx(+) Müller cells in the retina. There was an increase in RGC death in the glaucomatous eye following ONH-NPC depletion compared to control animals with elevated IOP but without ONH-NPC loss. No significant differences in RGC death were seen in eyes with ONH-NPC depletion compared to eyes without NPC depletion when IOP remained normal.
The approach enables selective depletion of ONH-Hopx(+)NPCs. The loss of these cells correlates with ONH-NPC depletion seen in aged mice and is similar to depletion of ONH-NPCs seen in aging humans. The ability to selectively deplete this cellular niche allows us to examine the effects of ONH-NPC elimination on various retinal and ON functions and to understand the

effects of their age-dependent loss on optic nerve diseases associated with aging.

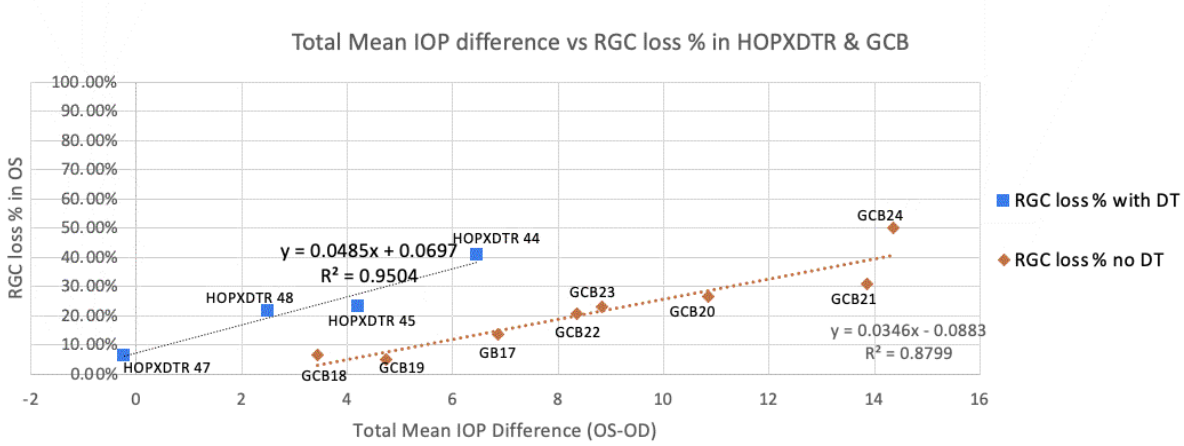


Figure 1. Elimination of ONLR-NPCs increases RGC Loss in a Mouse Glaucoma Model

Disclosures: J. Jouffroy: None. **S. Bernstein:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.21/T25

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG075440

Title: A Single Intranasal Dose of Extracellular Vesicles from hiPSC-NSCs in Early Middle Age Can Restrain Multiple Neuroinflammatory Signaling Networks Until Old Age

Authors: *M. KODALI, A. SAHITHI, G. SHANKAR, V. RAO, S. RAO, L. N. MADHU, A. K. SHETTY;
Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Sch. of Medicine, Te, College Station, TX

Abstract: Brain aging is typified by progressive cognitive decline linked with chronic low-grade sterile inflammation. Extracellular vesicles (EVs) from human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSCs) contain miRNAs and proteins that modulate neuroinflammation. We found that a single intranasal dose of hiPSC-NSC-EVs (10×10^9 EVs per dose) administered to 12-month-old C57BL6 mice (i.e., during early middle age) preserved cognitive functions in old age (i.e., at 19-20.5 months of age). To investigate the underlying anti-inflammatory mechanisms, transcriptomic profiling of the cerebral cortex was conducted in the aged-Veh and aged-EVs groups at 20.5 months of age using the NanoString nCounter Neuroinflammation Panel. Total RNA was isolated, converted to cDNA, and analyzed using a barcode-based system quantifying 756 genes involved in neuroinflammatory pathways.

Differential expression analysis identified 96 genes ($p < 0.05$). Pathway enrichment analysis revealed 75 significantly enriched pathways ($p<0.05$), including 52 highly significant pathways ($p<0.01$), of which 15 were directly related to inflammation. Key signaling pathways included tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), retinoic acid-inducible gene I (RIG-I)-like receptor, toll-like receptor (TLR), cytokine-cytokine receptor interactions, C-type lectin receptor, NOD-like receptor (NLR), interleukin (IL)-17, cytosolic DNA sensing, chemokine-chemokine interaction, adipocytokine, Ras, Advanced Glycation End-products Receptor for Advanced Glycation End-products (AGE-RAGE) signaling associated with diabetic complications, and sphingolipid signaling. All differentially expressed genes within TLR, NF-κB, adipocytokine, chemokine, C-type lectin receptor, IL-17, sphingolipid, and AGE-RAGE signaling pathways were downregulated following hiPSC-NSC-EVs treatment. The expression of most genes was significantly reduced in other signaling cascades, including NLR (6/7), Ras (5/6), MAPK (10/11), TNF (8/10), cytokine-cytokine interaction (6/9), cytosolic DNA sensing (3/4), and RIG-I-like receptor (5/6) pathways. These results suggest that a single dose of hiPSC-NSC-EVs in early middle age can restrain multiple neuroinflammatory gene networks in the aging brain for extended periods by attenuating multiple convergent inflammatory cascades. Thus, hiPSC-NSC-EVs treatment could be useful as a prophylactic to mitigate age-related neuroinflammation and preserve cognitive function.

Disclosures: M. Kodali: None. **A. Sahithi:** None. **G. Shankar:** None. **V. Rao:** None. **S. Rao:** None. **L.N. Madhu:** None. **A.K. Shetty:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.22/T26

Topic: C.01. Brain Wellness and Aging

Support: FAPESP 2022/09277-4
INCT: 25/26861-0
INCT/FAPESP: 2025/26861-0
FAPESP: 2023/02046-0
FAPESP: 2024/08685-7
FAPESP: 2024/06017-7

Title: Aging-Associated Hippocampal Dysfunction: Restorative Effects of Chronic Caffeine in the Senescence-Accelerated Mouse Model

Authors: *G. S. VILAR HIGA[1,2,3], F. VIANA[1,2], F. S. BORGES[5], A. KIHARA[4], R. DE PASQUALE[2], H. ULRICH[1];
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Matemática, Computação e Cognição, Univ. Federal do ABC, São Paulo, Brazil; [5]Dept. of Physiol. and Pharmacol., State Univ. of Ponta Grossa, Ponta Grossa, Brazil

Abstract: Aging progressively disrupts homeostasis and promotes cognitive decline by altering vulnerable brain regions such as the hippocampus. Age-related hippocampal dysfunction manifests at multiple levels, modifying neuronal excitability to cognition. Despite substantial knowledge, some aspects of functional changes and alterations in aged hippocampal neurons and the hippocampal network remain unclear. In this context, adenosine, a key neuromodulator that adjusts neuronal excitability and synaptic transmission, is significantly altered in the aging hippocampus. Caffeine, a widely consumed psychostimulant that primarily acts by antagonizing adenosine receptors and thereby the adenosinergic signaling pathway, has increasingly been associated with improved cognitive performance and a reduced risk of neurodegenerative conditions. Nevertheless, the mechanisms underlying caffeine effects on hippocampal aging remain unclear. Here, we employed the senescence-accelerated mouse model (SAMP8) to investigate the impact of aging on hippocampal function by evaluating pyramidal neuronal excitability, synaptic communication and plasticity, neuronal morphology, adenosine receptors, and the hippocampal neuronal network. We also investigated the role of long-term caffeine intake on aged hippocampal function. We observed that aged CA1 pyramidal neurons exhibited reduced excitability, altered excitation/inhibition balance, impaired synaptic plasticity, diminished A1 receptor function, diminished dendritic extension, and reduced reverberatory and integrative activity within the local network. Remarkably, chronic caffeine intake reversed several of these alterations, reorganized and improved the hippocampal network dynamics, and enhanced cognitive performance during aging. These findings provide mechanistic insights into how age affects the hippocampus and network-level processes, and how habitual caffeine consumption alleviates these effects, highlighting its potential as a therapeutic strategy to mitigate age-related cognitive decline.

Disclosures: G.S. Vilar Higa: 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.; FAPESP 2022/09277-4. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); FAPESP 2024/06017-7, INCT/FAPESP 2025/26861-0, INCT/CNPQ 409156/2024-8. **F. Viana:** 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.; INCT/FAPESP 2025/26861-0, FAPESP 2023/02046-0, INCT/CNPQ 409156/2024-8, CAPES. **F.S. Borges:** 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.; CNPq 446688/2024-0, CNPq 315055/2025-1. **A. Kihara:** A. Employment/Salary (full or part-time):; Universidade Federal do ABC. **R. De pasquale:** A. Employment/Salary (full or part-time):; Universidade de São Paulo. 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.; INCT/FAPESP 2025/26861-0, FAPESP 2023/02046-0, INCT/CNPQ 409156/2024-8. **H. Ulrich:** A. Employment/Salary (full or part-time):; Universidade de São Paulo. 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.; INCT/FAPESP 2025/26861-0, INCT/CNPQ 409156/2024-8. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); FAPESP 2024/06017-7.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.23/T27

Topic: C.01. Brain Wellness and Aging

Support: ERC StG OligoAging
ISF 1870/24

Title: An unbiased analysis of the myelin proteome in aged mice

Authors: *T. IRAM[1], A. KELLER[2], T. WYSS-CORAY[3];
[1]Weizmann Inst. of Sci., Rehovot, Israel; [2]Saarland Univ., Saarbruecken, ; [3]Stanford Univ., Stanford, CA.

Abstract: Myelin, once regarded as a static insulating structure, is now recognized as a dynamic component of the nervous system, capable of remodeling in response to experience. Its breakdown is linked to cognitive decline and neurodegenerative diseases, often preceding neuronal dysfunction. While the myelin proteome has been studied, the age- and sex-related changes it undergoes remain poorly understood. In this study, we purified myelin proteins from young, middle-aged, and aged male and female mice. Using mass spectrometry-based proteomics, we identified 4,095 unique proteins in males and 3,931 in females, with 1,121 proteins showing significant age-related changes in males and 1,251 in females. We find an age-related increase in compact myelin structural proteins, such as MBP, MOBP, and CLDN11, and a selective vulnerability in non-compact myelin cytoskeletal proteins, such as SEPTIN2, SEPTIN8, and TUBB4A. Notably, disease-associated proteins previously characterized in single-cell transcriptomics appear at the protein level in aged myelin. Yet, biochemical purification of myelin membranes might be contaminated by adjacent cellular compartments, such as axonal proteins and other light membrane compartments with similar biochemical properties. We therefore leverage biorthogonal non-canonical amino acid tagging (BONCAT) of nascent oligodendrocyte proteins *in vivo* to gain confidence in oligodendrocyte-derived proteins in the total myelin proteome dataset. Focusing on BONCAT-validated myelin proteins, we find a dramatic age-related increase in lysosomal and vesicle-associated proteins, while translation and synaptic proteins decrease in myelin with age in both sexes. This dataset highlights molecular mechanisms underlying the loss of myelin integrity and function with age and provides a novel tool for studying oligodendrocyte-derived nascent proteins *in vivo*.

Disclosures: T. Iram: None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.24/T28

Topic: C.01. Brain Wellness and Aging

Support: U19AG069701
R01AG087165

Title: Orchestrated multi-omic remodeling underlies brain aging

Authors: *Z. LI[1], Z. WANG[2], D. KONG[4], G. BU[5], J. PENG[3], N. ZHAO[6];
[1]Mayo Clin., Jacksonville, FL; [3]Structural Biol., [2]St. Jude Children's Res. Hosp., Memphis, TN; [4]St. Jude Children's Res. Hosp., Memphis, TN; [5]The Hong Kong Univ. of Sci. and Technol., Clear Water Bay, Hong Kong; [6]Neurosci., Mayo Clin. in Florida, Jacksonville, FL

Abstract: The brain preserves physiological integrity throughout most of the lifespan before losing homeostasis. Yet the underlying mechanisms remain unclear. Here, we performed multi-omic profiling of brains from mouse models expressing human *APOE* variants associated with longevity. We found that age is the predominant driver of proteomic, transcriptomic, and metabolomic alterations, largely independent of *APOE* genotypes. Proteins upregulated with age are enriched for small-molecule metabolism, aligning with age-related metabolomic shifts, whereas proteins involved in transcription, translation, and proteostasis are reduced. Notably, age-associated transcriptomic and proteomic changes are broadly concordant, with a subset of proteins displaying discordance. Machine learning suggests that these discrepancies are partially predicted by intrinsic sequence features associated with transcriptional and post-transcriptional regulation. Collectively, these findings suggest adaptive molecular remodeling during brain aging.

Disclosures: Z. Li: None. **Z. Wang:** None. **D. Kong:** None. **G. Bu:** None. **J. Peng:** None. **N. Zhao:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.25/T29

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 5T32DC000023
Kavli Neuroscience Discovery Institute Graduate Fellowship

Title: Aging selectively reduces molecular distinctions between auditory cortical subfields revealed by functionally registered spatial transcriptomics

Authors: *C. D. WORKMAN, P. GUO, J. M. KEBSCHULL, P. O. KANOLD;
Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Age-related hearing loss is accompanied by central deficits in complex sound processing, such as understanding speech in noise, but how aging alters auditory cortical molecular organization remains poorly understood. Defining these central molecular changes may explain why complex auditory processing declines even when peripheral hearing loss is limited or variable. Auditory cortical fields differ in sound tuning, connectivity, and processing roles, yet field boundaries vary between animals, making it difficult to relate molecular aging effects to functionally defined cortical regions. In this study, we combined functional mapping with spatial transcriptomics to examine subfield-specific aging effects in mouse auditory cortex. Widefield calcium frequency-response imaging identified primary (A1), anterior (AAF), secondary (A2), and dorsomedial (DM) auditory fields in adult and aged CBA/CaJ;Thy1-GCaMP6s mice, combining an age-stable hearing strain with cortical calcium reporting (aged P740-P778: 3 male, 3 female; adult P97-P333: 3 male, 3 female). DiI-marked functional boundaries were registered to serial tangential sections for 1000-gene BARseq3 spatial transcriptomics. More than 4 million cells from 12 mice were assigned cell types and analyzed for differential expression and molecular subfield identity.
Analyses revealed that aging-associated transcriptional remodeling was nonuniform across auditory subfields and cell classes. Age-associated gene-expression changes varied by cortical field, with prominent remodeling in low-latency AAF and comparatively weaker remodeling in integrative A2 across several major cortical populations, suggesting that auditory fields with distinct processing roles engage distinct molecular aging programs. To test whether these changes altered molecular distinctions between auditory fields, we also trained cell-type-specific linear discriminant analysis classifiers to distinguish functionally defined subfields and quantified pairwise molecular separability. Molecular subfield signatures were spatially organized within cell types and were altered with age in a subfield- and cell-type-dependent manner, with several excitatory, inhibitory, and non-neuronal populations showing age-associated reductions in molecular separability. Together, these results reveal spatially patterned and cell-type-specific remodeling of auditory cortical molecular organization with age, providing a framework for linking molecular aging to functional specialization in the brain.

Disclosures: C.D. Workman: None. **P. Guo:** None. **J.M. Kebschull:** None. **P.O. Kanold:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.26/T30

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant AG065168
NIDA Grant DA060630
NIMH Grant MH136297
NIMH Grant MH135895
NCCIH Grant AT010984
PRESTO JPMJPR2528
Foundation grants from Kanae
Mitsui sumitomo insurance welfare foundation
Cell science research foundation
Nakatomi Foundation
Wesco Science Foundation
Teraoka Memorial Foundation

Title: Glutamate-carboxypeptidase-II activation in astrocytes mediates glymphatic impairment and cognitive vulnerability in the aging brain following surgery

Authors: *H. KAWAI[1], Y. HASEGAWA[1], G. URSINI[4,1], F. XIONG[5], Y. LI[1], X. ZHU[1], T. SAWADA[4,2], B. S. SLUSHER[3,2], A. KAMIYA[1];
[1]Psychiatry and Behavioral Sci., [2]Neurol., [3]Drug Discovery, Johns Hopkins Univ., Baltimore, MD; [4]Lieber Inst. for Brain Develop., Baltimore, MD; [5]Icahn Sch. of Med. at Mount Sinai, New York City, NY

Abstract: Perioperative neurocognitive disorder (PND) is a common and debilitating complication in the elderly, yet its cellular and molecular mechanisms in the aging brain remain poorly understood. We examined the effects of abdominal surgery on cognition, glymphatic function, and astrocyte function focusing on sex-dependent mechanisms. We found that abdominal surgery induced male-specific deficits in recognition and spatial memory, reduced hippocampal glymphatic influx, and glutamate accumulation.These changes were associated with male-specific upregulation of glutamate signaling in a distinct astrocyte subpopulation, enhanced astrocytic glutamate carboxypeptidase II (GCPII) activity, perivascular astrocyte swelling, and loss of aquaporin-4 (AQP4) polarization. Astrocyte-specific GCPII knockdown rescued cognitive deficits, consistent with pharmacological GCPII inhibition ameliorating glutamate levels, AQP4 polarization, and cognitive performance. Together, our results identify astrocytic GCPII-mediated glutamate dysregulation as a key mechanism contributing to sex-specific postoperative cognitive vulnerability in the aging brain.

Disclosures: H. Kawai: None. **Y. Hasegawa:** None. **G. Ursini:** None. **F. Xiong:** None. **Y. Li:** None. **X. Zhu:** None. **T. Sawada:** None. **B.S. Slusher:** None. **A. Kamiya:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.27/T31

Topic: C.01. Brain Wellness and Aging

Title: Investigating the role of TF-RBP interactions in shaping sex-specific alternative splicing in the brain

Authors: *B. N. SAPOUNAS[1], N. HARISH[1], J. PULIDO[1], J. POUOKAM[1], D. RIVAS[1], D. BADHWAR[1], C. KAPETANAKOS[1], M. RAY[1,2];
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Abstract: Alternative splicing (AS), largely responsible for proteomic and organismal complexity, is most prevalent in neural tissue[1]. How RNA processing proteins locate target sites within the tightly packed nucleus in a conserved, sex-dependent manner remains unclear. We investigate the targeting of factors regulating AS in male and female *Drosophila* to determine the cellular context of sex-specific (SS) AS, providing a model for understanding RNA targeting in the brain. Considering many transcription factors (TF) and RNA-binding proteins (RBP) interact and have specific DNA and RNA motifs, we hypothesize that specific TF-RBP pairs interact to drive SS AS targeting. In *Drosophila*, Chromatin-Linked Adapter for MSL Proteins (CLAMP), is a DNA/RNA-binding TF, that binds and regulates SS RNA splicing[2]. CLAMP has an intrinsically disordered region (IDR) called the Prion-Like Domain (PrLD), essential for its binding to RNA targets and regulation of SS cryptic splicing events. But, it is unclear how the PrLD domain shapes the targeted processing of RNA molecules. Additionally, CLAMP binds the RBP Maleless (MLE), human homolog DHX9, in males via the dosage compensation complex[3]. Both MLE and DHX9 are RNA helicases and conserved components of the spliceosome complex[4]. CLAMP and MLE have both been shown to be important in neurogenesis and neuronal function. However, outside of the male-specific CLAMP-MLE interaction, the role of the CLAMP-MLE interaction in regulating brain-specific RNA processing, and subsequent effects on neuronal function, remains unknown. We first investigated the functional roles of the CLAMP PrLD domain and MLE protein in the brain using fly lines generated via CRISPR-Cas9, optogenetics, and RNAi. Climbing assays reveal that both CLAMP and MLE are required for neuro-motor function in males and females, where reduced function is seen with age. Additionally, loss of MLE in neurons, more than glia, results in a reduced male-to-female ratio, negatively impacting males, and lifespan assays show reduced male longevity. To determine CLAMP and MLEs role in AS of the SS neural transcriptome, we performed direct long-read sequencing (dLR-seq) using RNA extracted from male and female cell lines and brains. Our dLR-seq data from the cell lines indicates that MLE expresses a longer isoform in males compared to females. Further validation and assessment on the transcriptional and translational effects of CLAMP and MLE, via qPCR and western blot analysis, confirm SS splicing events. Overall, our study shows that the CLAMP and MLE pair target RNA transcripts, resulting in a SS splicing event in the brain.

Disclosures: B.N. Sapounas: None. **N. Harish:** None. **J. Pulido:** None. **J. Pouokam:** None. **D. Rivas:** None. **D. Badhwar:** None. **C. Kapetanakos:** None. **M. Ray:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.28/T32

Topic: C.01. Brain Wellness and Aging

Support: NSF Grant

Title: The Impacts of Intestinal Barrier Dysfunction on Brain and Muscle Aging

Authors: H. MOORE[1], O. HENKE[2], D. FOMBY[2], S. LE[2], ***A. SALAZAR**[2];
[1]Christopher Newport Univ., Mechanicsville, VA; [2]Christopher Newport Univ., Newport News, VA

Abstract: Declines in muscle and neuronal function are known correlates of aging. A clearer understanding of the pathophysiological changes accompanying aging, and the discovery of novel therapeutics to assist in aging phenotypes, are, therefore, essential. Recent advances have implicated perturbations in the gut as being closely linked to aging and mortality, with intestinal barrier dysfunction associated with age-related health decline in numerous organisms, including humans. Previous experiments have revealed that perturbed occluding junction expression in *Drosophila* intestines leads to various hallmarks of aging, with the loss of a specific occluding junction, Snakeskin (Ssk), leading to rapid and reversible intestinal barrier dysfunction, altered gut morphology, dysbiosis, elevations in immune activity, and a dramatically reduced lifespan. Remarkably, restoration of Ssk expression in flies showing intestinal barrier dysfunction reverses each of these phenotypes previously linked to aging. Intestinal up-regulation of Ssk protects against microbial translocation, improves intestinal barrier function during aging, limits dysbiosis, and extends lifespan. This study reveals that the genetic knockdown of Ssk leads to a highly significant increase in ubiquitinated protein aggregates and mitochondrial dysfunction in the *Drosophila* thorax muscles and brains of young flies, analogous to phenotypes observed in aged flies. Both of these known hallmarks of aging are associated with diseases such as Alzheimer's and Parkinson's Disease, and reveal that perturbing the gut in a young organism is sufficient to induce aging phenotypes in tissue outside the gut, including aging in the brains and muscles. These elevations in protein aggregates and mitochondrial dysfunction observed in young flies accompanying induced intestinal permeability recapitulate phenotypes observed in aged flies, revealing a tight connection between intestinal barrier dysfunction and brain and muscle aging. Current results investigate mechanisms driving muscle and brain aging through altering the intestinal barrier, with the ultimate goal of developing novel human therapies to extend healthspan.

Disclosures: H. Moore: None. **O. Henke:** None. **D. Fomby:** None. **S. Le:** None. **A. Salazar:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.29/U1

Topic: C.01. Brain Wellness and Aging

Support: Grant number JPJ013268 from the Acquisition, Technology &Logistics Agency(ATLA)

Title: LOW-DOSE BMAA INDUCES DNA DAMAGE AND A PRE-SENESCENT STATE IN HUMAN NEURONS

Authors: *K. HIRANO, M.-N. KHINE, Y. EBINA, R. WADHWA;
Natl. Inst. of Advanced Industrial Science, AIST, Tsukuba, Japan

Abstract: β-N-methylamino-L-alanine (BMAA) is a non-proteinogenic amino acid produced by cyanobacteria, known to exhibit neurotoxicity. Structurally, BMAA differs from alanine by a methylamine substitution at the β-carbon, which influences its biological behaviour. BMAA has been detected in the brains of patients with neurodegenerative diseases, including Alzheimer's disease. Although BMAA is commonly used at high concentrations to model neurodegeneration, the effects of low-dose exposure remain poorly understood. In this study, we investigated whether nanomolar concentrations of BMAA induce cellular stress responses in human neurons differentiated from induced pluripotent stem cell (iPSC)-derived neural stem cells, as well as in three-dimensional cerebral organoid models. Exposure to BMAA at concentrations up to 1000 nM did not affect the neuronal morphology. However, a significant increase in γ-H2AX, a marker of double-strand breaks (DSBs), was detected in low-dose BMAA-treated neurons, indicating DNA damage at low concentrations. This effect was not associated with increased reactive oxygen species (ROS) production, suggesting a ROS-independent mechanism. Further analysis revealed upregulation of the cell-cycle inhibitors p21 and p16, enhanced H3K9 methylation, a hallmark of senescence-associated heterochromatin foci (SAHF), and increased expression of amyloid precursor protein (APP), a precursor of amyloid-β (Aβ). In contrast, classical senescence markers, including components of the senescence-associated secretory phenotype (SASP), SA-beta-Gal activity, and Lamin B1 expression, were not significantly altered. These results indicate the induction of an intermediate cellular state rather than full senescence. We defined this state as a "neuronal pre-senescence" state. Collectively, these findings demonstrate that low-dose BMAA induces DNA damage and promotes a neuronal pre-senescence phenotype in human neurons, providing insight into early pathogenic events that may contribute to sporadic neurodegeneration.

Disclosures: K. Hirano: None. **M. Khine:** None. **Y. Ebina:** None. **R. Wadhwa:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.30/U2

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

Support: NIH R01 AG087945
NIH T32 AG049688

Title: Cross-species validation for highly multiplexed immunofluorescence imaging in the neocortex of orangutans, gorillas, bonobos, chimpanzees, and humans

Authors: E. MCDONOUGH[1], S. ABATE[1], I. PAINE[2], B. WICINSKI[3], W. HOPKINS[4], C. SHERWOOD[5], M. K. EDLER[6], M. RAGHANTI[7], D. MEYER[1], P. R. HOF[3], ***M. T. VARGHESE**[8];
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Abstract: The great apes, our nearest living relatives, show many similarities to humans as they age. In the brains of orangutans, gorillas, bonobos, and chimpanzees, these similarities include neuropathological changes such as amyloid-beta plaques, cerebral amyloid angiopathy, intracellular and neuritic deposits of tau, and age-related cognitive decline. We are investigating whether age-related changes in cellular responses in the brain occur that occur across these species correlate with the presence of cardiovascular or cerebrovascular disease in a similar manner. Towards this end, we are applying highly multiplexed immunofluorescence imaging on the dorsolateral prefrontal cortex (DLPFC) and the middle temporal gyrus (MTG) from great apes and humans across the lifespan and in the presence or absence of cardiovascular or cerebrovascular disease. Here, we present our preliminary findings on specimen quality control on the DLPFC and MTG and antibody validations on specimens from the primary visual cortex (V1). We have conducted morphological and staining quality checks on the curated set of specimens from nonhuman primates. A subset of specimens from the V1 of all species was used to create a tissue microarray for more extensive antibody validations. Markers for the major cell types, including HUD for neurons, ALDH1L1 and GFAP for astrocytes, IBA1 for microglia, Olig2 for oligodendrocytes, and Collagen IV and CD31 for vasculature showed strong signal. We observed variability in the detection of phosphorylated tau, such as Tau231, with robust signal in the human V1 and less so in V1 from the other great apes. Further cross-species validations are ongoing for markers associated with various neuronal subpopulations, glial cell states, infiltrating macrophages, and cardiovascular disease risk. This will be followed by testing for round-to-round antigen effects before expanding the study to the DLPFC and MTG to address our research question on the cellular factors contributing the susceptibility or resilience of these brain regions to aging across the great apes.

Disclosures: E. McDonough: A. Employment/Salary (full or part-time):; GE HealthCare. **S. Abate:** A. Employment/Salary (full or part-time):; GE HealthCare. **I. Paine:** None. **B. Wicinski:** None. **W. Hopkins:** None. **C. Sherwood:** None. **M.K. Edler:** None. **M. Raghanti:** None. **D. Meyer:** A. Employment/Salary (full or part-time):; GE HealthCare. **P.R. Hof:** None. **M.T. Varghese:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.31/U3

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R21AG080216

Title: Vulnerability of the chimpanzee cholinergic system to aging and Alzheimer's disease-like pathology

Authors: *C. HEARN[1], C. SHERWOOD[2], P. R. HOF[3], M. RAGHANTI[1], M. K. EDLER[1]; [1]Sch. of Biomed. Sci., Kent State Univ., Kent, OH; [2]George Washington Univ., Washington, DC; [3]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Alzheimer's disease (AD) is an irreversible neurodegenerative disorder and a leading cause of dementia in elderly populations. The cholinergic system regulates memory, concentration, and consciousness, and decline of this system in aging and AD contributes to memory loss and cognitive deficits in humans. The pathologic hallmarks of amyloid-beta (Aβ) plaques, cerebral amyloid angiopathy (CAA), and tau-associated neurofibrillary tangles (NFT) occur sporadically in elderly chimpanzees. Whether age or AD-like lesions impact the cholinergic system of chimpanzees has yet to be characterized. Here, we investigated the effects of aging, CAA, and NFT on the cholinergic system of 37 chimpanzees (16-51 years). Stereology was used to quantify the ratios of Nissl-stained glial density/neuron density (Gv/Nv), choline acetyltransferase-immunoreactive (ir) axon length density/neuron density (ChAT-ir ALv/Nv), ChAT-ir ALv/Nissl Nv, and ChAT-ir/Nissl Nv in the caudate nucleus (CN) and putamen (Put), while Gv/Nv and ChAT-ir/Nissl Nv were collected in the nucleus basalis of Meynert (NBM). ANCOVAs with age and sex*age interaction included as covariates were conducted in controls negative for CAA or neocortical (NC) NFT (N = 20: 12 males, 8 females). Gv/Nv was decreased in aged males in the NBM (sex: p=0.012, age: p=0.006, sex*age: p=0.010) and CN (sex: p=0.021, age: p=0.009, sex*age: p=0.004), while Gv/Nv was increased in aged females in the CN. ChAT-ir/Nissl Nv decreased with age in females in the NBM (sex: p=0.036, age: p=1.00, sex*age: p=0.037), while ChAT-ir ALv/Nv declined with age in males in the CN (sex: p =0.055, age: p=0.024, sex*age: p=0.039). Ratios were not affected by age or sex in the Put. For analysis of AD-related lesions, Welch's T-tests or Mann-Whitney tests were performed in female chimpanzees only, due to scarcity of pathology in aged males. Females were assigned to two cohorts: age-matched (33-59y) individuals with no or minimal CAA and no NC NFT (N=6) and those with moderate to severe CAA and NC NFT (N=6). We found that female chimpanzees with NFT and CAA had significantly lower Gv/Nv (p=0.0157) and significantly decreased ChAT-ir ALv/Nv (p=0.0303) ratios in the CN compared to individuals without pathology. Overall, the NBM and the CN of chimpanzees appear to be impacted in aging, while only the CN was affected by AD-like pathology. These results differ from what has been established in humans, where AD and aging are associated with decline of cholinergic function within NBM, while the CN is largely spared. This suggests divergent mechanisms between humans and chimpanzees in response to both aging and AD-associated pathology.

Disclosures: C. Hearn: None. **C. Sherwood:** None. **P.R. Hof:** None. **M. Raghanti:** None. **M.K. Edler:** None.

Poster

PSTR218: Brain Wellness and Aging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR218.32/U4

Topic:

Support: R01 AG087945
R01 AG078755
R01 AG067419
P30 AG066514

Title: Altered Cerebral White and Gray Matter Volumes during Aging and Vascular Disease in Great Apes

Authors: *I. PAINE[1], L. M. FARR[2], J. IGLESIAS GONZALEZ[3], W. D. HOPKINS[4], C. C. SHERWOOD[5], M. K. EDLER[6], M. RAGHANTI[7], M. T. VARGHESE[8], P. R. HOF[1]; [1]Icahn Sch. of Med., New York, NY; [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York City, NY; [3]Massachusetts Gen. Hosp., Charlestown, MA; [4]The Univ. of Texas MD Anderson Cancer, Bastrop, TX; [5]George Washington Univ., Washington, DC; [7]Dept Anthropol & Sch. Biomed Sci., [6]Kent State Univ., Kent, OH; [8]George & Anne Ryan Inst. for Neuroscience, Dept. of Biomed. and Pharmaceut. Sci., Univ. of Rhode Island, Kingston, RI

Abstract: Aging is a primary risk factor for cerebrovascular (CeVD) and cardiovascular diseases (CaVD), which are frequently associated with cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD). Neuronal loss, cognitive decline, and brain atrophy are correlated but how vascular disease may exacerbate these age-related deficits is not well understood. Great apes are valuable models of aging because they have long life spans and display age-related pathologies in the brain and heart that are comparable to those in humans. Comparative studies between humans and great apes can also reveal human-specific resilience and/or susceptibilities in the context of age-related diseases. Ex vivo magnetic resonance imaging (MRI) scans of chimpanzee and gorilla brains were analyzed for changes in cerebral grey and white matter across lifespan in vascular disease. Chimpanzees were grouped into young (n=10), middle-aged (n=22), and elderly (n=16) individuals without vascular disease, as well as individuals with CeVD (n=25), and CaVD (n=9). Gorillas were grouped into young/middle-aged (n=10), elderly (n=11), and CaVD (n=14). MRI scans were segmented using the SuperSynth tool in FreeSurfer. SuperSynth is a neural network trained on human brains, which are fundamentally similar to great ape brains in terms of overall layout and cellular architecture. Volumes for cerebral grey and white matter were log-transformed and modeled as a function of log-transformed whole cerebral hemisphere volume, study group, sex, and hemisphere, with subject included as a random intercept. Pairwise differences of the estimated marginal mean volumes

between groups were evaluated using Tukey-adjusted comparisons. Preliminary analysis in chimpanzees showed that cerebral cortex volume is significantly decreased in the CeVD group compared to young (p=0.01) and elderly (p=0.03) controls. Cerebral cortex volume is also decreased in the CaVD group compared to young controls (p=0.04). Conversely, cerebral white matter volume was significantly increased in the CeVD group compared to both young controls (p=0.03). Preliminary analysis in gorillas shows no significant differences, but a decreasing trend in cerebral cortex in the CaVD group compared to young/middle-aged controls. Ongoing work is examining potential changes in cortical thickness across different regions in the cortex in the same cohorts. The lack of change in cerebral gray or white matter with age is consistent with studies examining whole brain volume changes with age in humans and chimpanzees. In chimpanzees, CeVD and CaVD may worsen mild cortical shrinkage that occurs with age.

Disclosures: I. Paine: None. **L.M. Farr:** None. **J. Iglesias Gonzalez:** None. **W.D. Hopkins:** None. **C.C. Sherwood:** None. **M.K. Edler:** None. **M. Raghanti:** None. **M.T. Varghese:** None. **P.R. Hof:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.01/U5

Topic: C.01. Brain Wellness and Aging

Title: Neuroprotective Effects of Fucoxanthin in Experimental Models of Mitochondrial Dysfunction

Authors: *K. WON[1], H.-A. PARK[2];
[1]The Univ. of Alabama, Tuscaloosa, AL; [2]Univ. of Alabama, Tuscaloosa, AL

Abstract: Mitochondrial dysfunction contributes to oxidative stress, metabolic dysfunction, and neuronal death, and is implicated in neurodegenerative diseases. Fucoxanthin, a marine carotenoid abundant in brown seaweed, exhibits antioxidant and neuroprotective properties. In this study, we hypothesized that treatment with fucoxanthin prevents neuronal injury associated with mitochondrial dysfunction. Middle-aged male Sprague-Dawley rats received fucoxanthin (1 mg/kg) or vehicle by oral gavage for 4 weeks. Following supplementation, animals were euthanized after transcardial perfusion, and brain tissue was collected for analysis. Fucoxanthin was detected in brain tissue from fucoxanthin-supplemented animals compared with controls. Transcriptomic profiling of whole-brain tissue showed that oral supplementation of fucoxanthin upregulated 2,666 genes and downregulated 2,936 genes. Notably, proteins that control oxidative stress and mitochondrial function such as DJ-1 and Bax are significantly regulated by fucoxanthin. To evaluate the effects of fucoxanthin under mitochondrial dysfunction, primary hippocampal neurons were exposed to rotenone, a mitochondrial complex I inhibitor, in the presence or absence of fucoxanthin. Rotenone increased PI-positive dead cells, whereas fucoxanthin attenuated rotenone-induced cell death. Together, these findings demonstrate that

orally administered fucoxanthin reaches the brain, alters gene and protein expression in brain tissue *in vivo*, and prevents neuronal cell death-associated with mitochondrial dysfunction *in vitro*. We further expand our investigation by measuring mitochondrial superoxide levels, mitochondrial membrane potential, and the ATP/ADP ratio to characterize the effects of fucoxanthin on mitochondrial function.

Disclosures: K. Won: None. **H. Park:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.02/U6

Topic: C.01. Brain Wellness and Aging

Support: School of Pharmacy - Boston, Department of Pharmaceutical Sciences

Title: Mechanistic investigation of Gymnemic Acid - I (GA-1) in differentiated SH-SY5Y cells

Authors: *M. M. SHAH[1], M. M. MIGLIORE[2];
[1]Massachusetts Col. Of Pharm. And Hlth. Sci. (MCPHS University), Boston, MA;
[2]Massachusetts Col. Of Pharm. and Hlth. Sci., Boston, MA

Abstract: Nearly 1 out of 8 individuals in the United States is affected by diabetes mellitus (DM), of which approximately 90-95% of cases are attributed to Type 2 (T2DM), a major metabolic disorder resulting from impaired insulin production and/or reduced insulin sensitivity. T2DM causes chronic hyperglycemia and dysregulated energy metabolism, ultimately contributing to long-term cellular and tissue damage across multiple organ systems. Diabetic neuropathy, characterized by progressive neuronal damage and pain, is among the most debilitating complications. *Gymnema sylvestre*, an anti-diabetic medicinal plant traditionally used in Ayurvedic medicine for glucose regulation, has emerged as a potential neuroprotective candidate. Previous studies conducted in our laboratory demonstrated the neuroprotective potential of Gymnemic Acid-I (GA-1), a major bioactive constituent of *Gymnema sylvestre*, in undifferentiated SH-SY5Y cells. Building upon these findings, the present study provides a mechanistic evaluation of GA-1 in differentiated neuronal SH-SY5Y cells, thereby offering a more physiologically relevant *in vitro* model for investigating diabetic neuropathy. To further validate the therapeutic potential of GA-1, its cytotoxic profile and neuroprotective efficacy were evaluated in differentiated SH-SY5Y neuronal cells. GA-1 (10μM-80μM) exhibited no significant decrease in cell viability, confirming the absence of inherent toxicity. Neurotoxicity was induced using 6-hydroxydopamine (6-OHDA) and streptozotocin (STZ),which model oxidative stress-mediated neuronal damage and diabetic neuropathy, respectively. The IC_{50} value for 6-OHDA was determined to be 40 μM and that of STZ was3.5 nM with statistical significance ($p<0.05$) through One-Way ANOVA. Considering the established role of GA-1 in glucose homeostasis, insulin production was investigated as a potential mechanism using an

insulin ELISA initially in undifferentiated SH-SY5Y cells. GA-1 treatment groups did not exhibit insulin levels above control, indicating that GA-1's neuroprotection is not insulin-mediated in this cell line. Consequently, this investigation was not extended to differentiated SH-SY5Y cells. Current studies are focused on evaluating oxidative stress and the involvement of the advanced glycation end products (RAGE) signaling pathway. These studies aim to further elucidate the molecular mechanisms underlying the neuroprotective effects of GA-1 in differentiated SH-SY5Y neuronal cells and its potential therapeutic relevance in diabetic neuropathy.

Disclosures: M.M. Shah: None. **M.M. Migliore:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.03/U7

Topic: C.01. Brain Wellness and Aging

Support: American Heart Association 25POST1374467
NIGMS R35 GM118141
VA Merit Award I01BX003303
University of Miami Neuro Team Science Award 2025

Title: Mitochondrial adaptation to neurological disease-relevant stress conditions

Authors: *A. SIERRA-MAGRO, J. LAVERDE-PAZ, Z. ZEIER, A. BARRIENTOS; Univ. of Miami, Miami, FL

Abstract: Neurological disorders are frequently associated with altered oxygen availability and redoximbalance, conditions that challenge mitochondrial function and neuronal homeostasis.Because mitochondria both consume oxygen and generate reactive oxygen species (ROS),they act as central sensors and eBectors of these stress responses. However, themechanisms by which mitochondria adapt their respiratory machinery and gene-expressionprograms to these stressors remain poorly understood.We investigated mitochondrial adaptation to disease-relevant stress using human cellmodels and biochemical, molecular, and quantitative proteomic approaches. First, weexamined remodeling of the mitochondrial respiratory chain (MRC), focusing on cytochrome*c* oxidase (complex IV; CIV), the terminal enzyme. CIV contains subunits with stress-responsive isoforms, including NDUFA4. In HEK293T cells exposed to sustained hypoxia orto oxidative stress induced by ectopic expression of D-amino acid oxidase (DAAO), weobserved robust transcriptional induction of the NDUFA4L2 and NDUFA4L3 isoforms.However, incorporation of these isoforms into mature CIV was limited, indicating that stress-induced expression alone is insuBicient to drive CIV isoform exchange and suggestingadditional constraints on respiratory-chain remodeling.Second, SILAC-based proteomics identified mitochondrial translation as one of theprocesses most

aBected by sustained oxidative stress. Given its essential role in thebiogenesis of the oxidative phosphorylation system, these findings suggest that regulationof mitochondrial gene expression constitutes a major adaptation to redox imbalance.Finally, we implemented the DAAO platform in human iPSCs to extend these studies toneuronal systems. This approach will enable controlled oxidative stress induction in adisease-relevant cellular context and provide a framework for investigating how oxygenavailability and redox imbalance influence MRC remodeling and mitochondrial geneexpression programs in neurons.Together, our findings support a multilayered model of mitochondrial adaptation to stressinvolving both MRC remodeling and regulation of mitochondrial gene expression, andestablish experimental platforms to investigate these processes in neurological diseasemodels.

Disclosures: A. Sierra-Magro: None. **J. Laverde-Paz:** None. **Z. Zeier:** None. **A. Barrientos:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.04/Web Only

Topic: C.01. Brain Wellness and Aging

Title: Reverse electron transfer and gut microbiome regulate sleep deprivation pathology in Drosophila

Authors: *Y. HE[1,2], J. LEE[2], B. LU[2];
[1]Stanford Univ., Menlo Park, CA; [2]Pathology, Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Sleep deprivation (SD) causes widespread physiological and cognitive decline across a wide range of species. Recent reports have shown that mitochondrial physiology and the gut microbiome are involved in the pathological outcomes resulting from SD; however, effective therapeutic strategies remain elusive. In this study, using Drosophila melanogaster, we aimed to elucidate the comprehensive consequences of SD and examine whether reverse electron transfer (RET) or the gut microbiome mediates these pathological processes. To investigate this, flies were first categorized by their SD status and then further subdivided into three dietary groups: 1) standard food, 2) food supplemented with CPT (a RET blocker), and 3) food supplemented with an antibiotic cocktail (axenic conditions). We subsequently analyzed these flies at the physiological, molecular, and behavioral levels, and found that both CPT and axenic conditions ameliorated multiple SD-induced deficits. In conclusion, these findings pave the way for identifying targetable physiological pathways for therapeutic interventions against SD.

Disclosures: Y. He: None. **J. Lee:** None. **B. Lu:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.05/U8

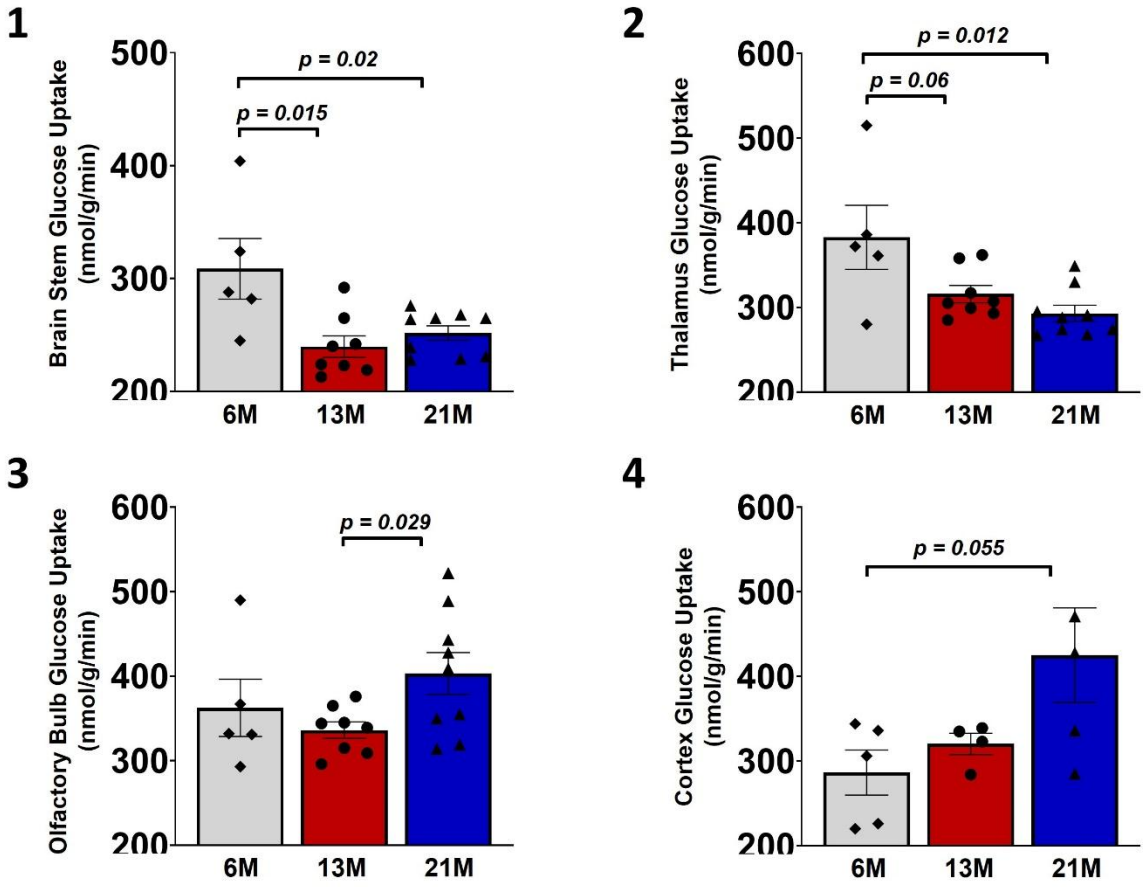
Topic: C.01. Brain Wellness and Aging

Support: National Institutes of Health R01-AG085308

Title: Differential Effects of Aging on Brain Glucose Metabolism in Mice

Authors: A. DARYANANI, G. HUR, M. SAJID, J. BOWMAN, F. HUSSAIN, A. JAYAMOHAN, D. DAVIS-ANAGBOSO, J. KINGHAM, S. HAARALA, A. MUÑOZ, O. FRIMPONG, H. D'URSO, A. CHUNG, J. RICKUS GARCIA, L. TAUER, P. MANN, ***J. K. KIM**;
Mol. Med., UMass Chan Med. Sch., Worcester, MA

Abstract: Glucose is a primary energy source for the brain, and despite weighing only 2% of the body weight, the brain accounts for ~25% of whole-body glucose consumption. While altered glucose metabolism is an early pathologic event in Alzheimer's brain, how aging affects different regions of the brain remains unclear. Using intravenous non-metabolizable glucose analog, [^{14}C]2-deoxyglucose in awake mice, we measured regional brain glucose uptake in male C57BL/6J mice at 6 (6M; n=5), 13 (13M; n=4-8), and 21-24 months of age (21M; n=5-9). Glucose metabolism in the brain stem (BS) decreased by 22% in 13M and 19% in 21M compared to 6M mice (Fig. 1). Glucose metabolism in the thalamus also reduced by 18% in 13M and 24% in 21M compared to 6M mice (Fig. 2). In contrast, glucose metabolism in the olfactory bulb was not altered in 13M and increased by 20% in 21M mice (Fig. 3). Glucose metabolism in the cerebellum (CB) was decreased by 10% with aging (279±21 nmol/g/min in 13M and 303±15 nmol/g/min in 21M vs. 310±25 nmol/g/min in 6M). Glucose metabolism in the hippocampus was also decreased by 8% with aging (225±18 nmol/g/min in 13M and 254±11 nmol/g/min in 21M vs. 244±20 nmol/g/min in 6M). Next, we performed a hyperinsulinemic-euglycemic clamp with labeled glucose to measure insulin-stimulated brain glucose uptake. Surprisingly, insulin-stimulated uptake in the cortex increased by 49% in 21M compared to 6M mice (Fig. 4). Insulin-stimulated glucose uptake in CB and BS also increased by 30% and 17% in 21M mice (345±44 nmol/g/min vs. 266±26 nmol/g/min in 6M mice for CB; 317±44 nmol/g/min vs. 271±24 nmol/g/min in 6M mice for BS). In conclusion, brain glucose metabolism mostly decreased in early aging and further decreased with advanced aging, whereas insulin-stimulated glucose uptake increased in aging mice. These results indicate that aging causes a progressive decline in brain glucose metabolism, and increased insulin action may be an adapted response to this deficit, supporting the notion that altered brain glucose metabolism may be an early pathologic event possibly leading to Alzheimer's disease in humans.



Disclosures: A. Daryanani: None. **G. Hur:** None. **M. Sajid:** None. **J. Bowman:** None. **L. Tauer:** None. **J.K. Kim:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.06/U9

Topic: C.01. Brain Wellness and Aging

Support: SECIHTI postgraduate scohlarship #4018907

Title: Obese phenotype on redox status, inflammatory balance, and hypothalamic glial phenotype in obese ZDF rats

Authors: *G. PULIDO-FERNANDEZ, S. TREVIÑO, A. HANDAL, J. MORAN PERALES, A. DIAZ;
BUAP, Puebla, Mexico

Abstract: Obesity is a chronic, multifactorial disease that poses a significant global health challenge, associated with a wide range of comorbidities. Central to the pathophysiology of these complications is the hypothalamus, a brain region that functions as the primary regulator of energy homeostasis. The hypothalamus integrates peripheral metabolic signals, such as leptin and insulin, to coordinate food intake, thermogenesis, and glucose metabolism. In the context of chronic overnutrition, the hypothalamus becomes a primary target of metabolic damage. It is proposed that inflammation and oxidative stress are the main mechanisms of damage in states of overnutrition. In this context, glial cells play a crucial role in the regulation of inflammation and oxidative stress. The aim of the present work is to evaluate the hypothalamic inflammatory/antinflamatory and oxidative balance in the obese Zucker Diabetic Fatty rat (OZDF), compared with a metabolic functional model. For this, 5 weeks old OZDF and Wistar rats were used. Animal were divided into four groups (n=8/group): 1) Wistar + LabDiet 5001, 2) Wistar + LabDiet 5008, 3) OZDF + LabDiet 5001 and 4) OZDF + LabDiet5008. The data were reported as the mean ± standard error (SE). A Two-Way ANOVA followed by a Dunnet post-test where $p < 0.05$ was considered significant. The results show increase in the proinflammatory factors evaluated in both OZDF groups compared with both Wistar groups. Nevertheless, the anti-inflammatory factors are elevated in the same trend in both the OZDF group. Whereas the oxidative markers are increased in the obese groups this change is not compensated by the activity of antioxidant enzymes nor the concentration of reduced gluthathione. These findings indicate that in this model, the expansion of adipose tissue does not impact the equilibrium between inflammatory and anti-inflammatory responses in the hypothalamus. However, it does alter the balance between oxidative and antioxidant responses. Our results suggest mechanisms regulated by glial cells that prevent or delay the development of inflammation but do not control oxidative stress.

Disclosures: G. Pulido-fernandez: None. **S. Treviño:** None. **A. Handal:** None. **J. Moran Perales:** None. **A. Diaz:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.07/Web Only

Topic: C.01. Brain Wellness and Aging

Support: CIC-U.M.S.N.H. 2026
ICTI-MICHOACAN-2026

Title: Effect of Hypercaloric diet on the sodium pump activity in cerebral cortex of rats.

Authors: *R. MERCADO[1], O. GUZMÁN-QUEVEDO, ex[2], S. RODRÍGUEZ[3];
[1]Univ. Michoacana, Tarimbaro, Michoacan, Mexico; [2]Inst. Tecnológico de Tacámbaro, Tacámbaro, Mexico; [3]UNIVERSIDAD MICHOACANA DE SAN NICOLÁS DE HIDALGO, Morelia, Mexico

Abstract: It is well known that diabetes mellitus (DM) is a disease strongly related to a high-calorie intake between other factors and also associated with metabolic syndrome. In previous results we show an increase in body weight in the group with glucose and fatty acids supplementation, also we previously observed that sodium pump activity was lower in the cerebral cortex of rats with experimental DM type I. So, the aim of the present work was to explore the effect of the supplementation with carbohydrates and lipids the normal diet rat during ten months on the sodium pump activity in the cerebral cortex of male and female Wistar rats. Results showed a reduction of the sodium pump activity in both groups. These data shows a correlation with the effect previously observed with of the experimental DM type I.

Disclosures: R. Mercado: None. **O. Guzmán-Quevedo:** None. **S. Rodríguez:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.08/U10

Topic: C.01. Brain Wellness and Aging

Support: SECIHTI CBF2023-2024-1641

Title: Diabetes Amplifies Hippocampal Glial Reactivity in Female CD-1 Mice Exposed to a Hypercaloric Diet

Authors: *A. LOMELI LEPE[1], S. J. LOPEZ-PEREZ[2];
[1]Univ. of Guadalajara, Zapopan, Mexico; [2]Cell and Mol. Biol., CUCBA-Universidad de Guadalajara, Zapopan, Jalisco, Mexico

Abstract: Diabetes Amplifies Hippocampal Glial Reactivity in Female CD-1 Mice Exposed to a Hypercaloric Diet
Metabolic disorders such as obesity and diabetes are associated with chronic neuroinflammation and increased risk of cognitive impairment. Glial cells play a central role in these processes; however, the combined effects of hypercaloric diet-induced metabolic stress and diabetes on hippocampal glial reactivity remain incompletely understood. This exploratory study investigated astrocytic and microglial responses in the hippocampus of female CD-1 mice subjected to a hypercaloric diet (HCD) and alloxan-induced diabetes.Female CD-1 mice were assigned to three groups (n=5/group): Control (fed a standard diet), HCD, and HCD+Alloxan (HCD+A). Animals received HCD for 4 weeks, after which diabetes was induced in the HCD+A group by two doses of alloxan (180 and 150 mg/kg) while maintaining the diet for an additional week. Animals were sacrificed by transcardial perfusion. Hippocampal sections were processed

for GFAP and Iba-1 immunofluorescence to assess astrocytic and microglial reactivity, respectively. Optical density was quantified in the dentate gyrus (DG), CA1, and CA3 hippocampal subregions. Control animals served as biological controls, and all tissues were processed, imaged, and analyzed under identical experimental conditions.HCD increased GFAP and Iba-1 immunoreactivity throughout the hippocampus compared with controls, indicating enhanced glial activation under metabolic challenge. Moreover, mice in the HCD+A group exhibited a further increase in GFAP and Iba-1 signal across the analyzed hippocampal regions relative to HCD alone, suggesting that diabetic conditions exacerbate neuroinflammatory responses beyond the effects of diet-induced metabolic stress.These findings demonstrate that the combination of HCD and alloxan-induced diabetes promotes pronounced hippocampal gliosis in female CD-1 mice. This model provides a useful platform for investigating mechanisms linking metabolic dysfunction, neuroinflammation, and brain vulnerability.

Disclosures: A. Lomeli Lepe: None. **S.J. Lopez-Perez:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.09/U11

Topic: C.01. Brain Wellness and Aging

Support: TCU College of Science and Engineering SERC Gran

Title: Diet-Induced Peripheral Alterations Associated with Alzheimer's Disease Risk and Gut-Liver-Brain Axis Dysfunction in C57BL/6J Mice

Authors: *L. S. EDDLEMAN[1], L. P. GUNDERSON[2], J. A. SUAREZ[3], G. W. BOEHM[4], M. J. CHUMLEY[1];
[1]Biol., [2]Psychology, [3]Texas Christian Univ., Fort Worth, TX; [4]TCU, Granbury, TX

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuroinflammation, and amyloid-β accumulation. While age remains the primary risk factor for AD, increasing evidence suggests that diet-induced metabolic dysfunction contributes significantly to disease onset and progression. Diets high in saturated fats and refined sugars promote obesity, oxidative stress, and chronic inflammation, which may compromise vascular integrity and facilitate the transmission of peripheral inflammatory signals to the brain via the gut-liver-brain axis. To investigate the relationship between dietary patterns and AD-associated risk factors, male and female C57BL/6J mice were maintained on either a Mediterranean-like diet (MED), a Typical American Diet (TAD), or standard chow for 6 months post-weaning. Histological analyses revealed substantial hepatic lipid accumulation in TAD-fed mice, accompanied by significantly increased liver weights in both male and female mice compared to MED-fed controls. TAD-fed mice also exhibited significantly greater white adipose tissue mass and adipocyte area, indicative of chronic metabolic stress and systemic dysfunction.

In contrast, MED-fed mice showed significantly higher goblet cell counts in the colon, suggesting enhanced intestinal barrier protection and mucosal health, whereas no significant differences were observed in small intestinal villus length. Furthermore, molecular analyses showed elevated hepatic expression of genes associated with oxidative stress, such as heme oxygenase-1, and with inflammation, such as TNF-α. Overall, these findings demonstrate that long-term consumption of a Typical American Diet promotes metabolic and inflammatory changes associated with established hallmarks of Alzheimer's disease, whereas a Mediterranean-like diet provides protective effects on peripheral health. These results support a mechanistic role for the gut-liver-brain axis in linking dietary habits to the risk of neurodegenerative disease and suggest that dietary intervention may be a viable strategy for reducing susceptibility to Alzheimer's disease.

Disclosures: L.S. Eddleman: None. **L.P. Gunderson:** None. **J.A. Suarez:** None. **G.W. Boehm:** None. **M.J. Chumley:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.10/U12

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant S10OD032451
NIH grant R01EY030747
Felix and Carmen Sabates Missouri Endowed Chair in Vision Research

Title: Oxidative stress in neural progenitor cells alters the expression of proteins involved in neuronal differentiation and survival uniquely at different developmental stages

Authors: *R. S. DUNCAN[1], S. M. RIORDAN[2], J. MACEK[1], S. JONES[3], P. KOULEN[4]; [1]Ophthalmology, Univ. of Missouri - Kansas City, Kansas City, MO; [2]Univ. of Missouri - Kansas City, Lenexa, KS; [3]Ophthalmology, Univ. of Missouri - Kansas City, Camden Point, MO; [4]Biomed. Sci. and Ophthalmology, UMKC, Kansas City, MO

Abstract: Neural progenitor cells (NPCs) can generate neurons and glia *in vitro* to allow the of study central nervous system differentiation and of neurodegenerative and neuroprotective processes. Since oxidative stress can contribute to the pathogenesis of neurodegenerative diseases, we determined whether the induction of oxidative stress *in vitro* by exposure to the oxidant, tert-butyl hydroperoxide, differentially affected the proteomes of NPCs across different cellular developmental stages. We used proteomics and subsequent protein expression and pathway analysis to identify proteins that were uniquely expressed based on differentiation status and under conditions of under oxidative stress. Our results consisted of over 7,800 candidate proteins from which we identified over 100 differentially expressed proteins involved in neuronal differentiation, morphological development, and neuroprotective responses across three

developmental stages and a subset of over 50 proteins that are also differentially expressed under conditions of oxidative stress. Our results provide insights into the mechanisms through which oxidative stress may affect the differentiation process of neurons as well as which cellular processes may be most affected by oxidative stress at a particular stage of differentiation. These results may have potential implications for the use of stem and progenitor cell-based therapies for neurodegenerative diseases.

Disclosures: R.S. Duncan: None. **S.M. Riordan:** None. **J. Macek:** None. **S. Jones:** None. **P. Koulen:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.11/U13

Topic: C.01. Brain Wellness and Aging

Support: São Paulo Research Foundation (FAPESP) Grant 2022-14961-1
São Paulo Research Foundation (FAPESP) Grant 2024/23570-1

Title: Oxidative Stress Resilience in iPSC-Derived CA3-Like Hippocampal Neurons From Cognitively Preserved and Alzheimer-Affected Centenarians

Authors: *M. SILVA;
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Abstract: Introduction: Extreme longevity provides a unique model to investigate mechanisms of neuronal resilience and vulnerability to neurodegeneration. Oxidative stress, impaired antioxidant responses, apoptosis, and DNA damage are features of aging and Alzheimer's disease, but whether cognitively preserved centenarians retain cell-intrinsic neuronal resistance to oxidative injury remains unclear. We investigated oxidative stress responses in iPSC-derived CA3-like hippocampal neurons from cognitively preserved centenarians and centenarians with presumed Alzheimer's disease. Methods: iPSC lines generated from centenarian women were differentiated into CA3-like hippocampal neurons and divided into two groups: cognitively preserved centenarians and centenarians with presumed Alzheimer's disease (n = 3 per group). Neurons were exposed to hydrogen peroxide to induce oxidative stress under standardized conditions: mild (25 μM); moderate (100 μM); and high stress (200 μM). Responses were evaluated after 2h, 6h, and 24h of exposure. Cell viability was evaluated by MTT assay, apoptosis by caspase activity, intracellular oxidative stress by the 2',7'-dichlorofluorescein diacetate (2,7-DCFH-DA) assay, DNA strand break-associated damage by the alkaline comet assay, and extracellular antioxidant response by total antioxidant capacity (TAC). Formaldehyde was included as a genotoxic positive control for the comet assay. Results: Hydrogen peroxide exposure induced a dose- and time-dependent oxidative stress response in iPSC-derived CA3-like hippocampal neurons. Compared with neurons derived from centenarians with presumed

Alzheimer's disease, neurons from cognitively preserved centenarians displayed a more resilient response to oxidative challenge. This was reflected by a coordinated pattern of improved stress tolerance, better preservation of cell viability, and more effective control of intracellular ROS accumulation. The 100 μM hydrogen peroxide condition at 6h produced the most consistent separation between groups, indicating differential neuronal vulnerability to oxidative injury. Conclusion: Together, iPSC-derived CA3-like hippocampal neurons, controlled hydrogen peroxide challenge, and this study provide an integrated functional platform to investigate stress-resilience phenotypes in cognitively preserved and Alzheimer-affected centenarians. These results reveal a biologically meaningful trend toward enhanced neuronal redox resilience in cognitively preserved centenarians and support the expansion of the sample size to validate these findings in a genetically diverse cohort.

Disclosures: M. Silva: None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.12/U14

Topic: C.01. Brain Wellness and Aging

Support: NIH AG072714
AFAR Grant
UF University Scholars Program
Center for Cognitive Aging and Memory

Title: Age-related changes in intraneuronal glucose availability in mPFC following systemic administration of glucose and insulin

Authors: *A. THACH[1], S. ZEQUEIRA[2], M. FARAJI[3], Z. KRUMM[2], S. N. BURKE[4], B. SETLOW[3], J. L. BIZON[2];
[2]Dept. of Neurosci., [3]Dept. of Psychiatry, [1]Univ. of Florida, Gainesville, FL; [4]Dept. of Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: Glucose is the primary energy source of the brain, and the main substrate that supports neural activity. Aging is associated with brain glucose hypometabolism, impaired substrate transport, and mitochondrial dysfunction. These metabolic impairments can hinder energy availability and may contribute to age-related cognitive decline.
Prior studies of cerebral glucose availability employed techniques such as positron emission tomography and microdialysis, which have limited temporal resolution and/or cannot be easily integrated with behavioral testing. Recently, however, developments in genetically-encoded biosensors have enabled these limitations to be circumvented. Specifically, fiber photometry paired with the genetically encoded glucose sensor iGlucoSnFR enables real-time visualization of intra-neuronal glucose dynamics at sub-second timescales in awake, behaving animals.

We used iGlucoSnFR to examine how glucose availability in the medial prefrontal cortex (mPFC) varies across age and metabolic challenge. Young adult (5 months) and aged (23 months) Fischer 344 × Brown Norway F1 hybrid rats underwent stereotaxic injection of pAAV.hSynap.(cyto)iGlucoSnFR-mRuby2 into the mPFC, followed by implantation of an optic fiber. Using a within-subjects design, rats received i.p. injections of glucose, insulin, or saline, and metabolic responses to these challenges were compared using insulin and glucose tolerance tests in the same rats. Fiber photometry signals assessed in each injection condition were acquired using an RZ10x system (Tucker-Davis Technologies). Fluorescence signals (ΔF/F) were aligned to injection onset and z-scored relative to pre-injection baseline periods. Responses for glucose tolerance tests saw aged rats exhibiting a more elevated peak glucose response compared to young rats, consistent with age-related impairments in peripheral glucose regulation. mPFC glucose levels increased after glucose injections and decreased after insulin injections for both groups. Age differences in glucose dynamics were seen following glucose injections, such that aged rats had more varied responses compared to young rats. Further investigation of this variance revealed two subsets within the aged group, with distinct glucose dynamics independent of body weight. Ongoing experiments are assessing how mPFC glucose levels vary as a function of cognitive load between young and aged rats.

Disclosures: A. Thach: None. **S. Zequeira:** None. **M. Faraji:** None. **Z. Krumm:** None. **S.N. Burke:** None. **B. Setlow:** None. **J.L. Bizon:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.13/U15

Topic: C.01. Brain Wellness and Aging

Support: NIH R01DK130913
AHA 24SFRNPCN1284390
the Sinai Medical Staff Foundation
the Robert E. Nederlander Sr. Program for Alzheimer's Research
the Andrea and Lawrence A. Wolfe Brain Health Initiative
the NeuroNetwork for Emerging Therapies

Title: Transfer of Phosphorylated JNK and ERK via Extracellular Vesicles: A Potential Mechanism Underlying the Development of Insulin Resistance in Recipient Neurons

Authors: *B. KIM[1], E. L. FELDMAN[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Neurol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Background: Metabolic syndrome (MetS) is characterized by insulin resistance, mitochondrial dysfunction, chronic inflammation, and oxidative stress. Diets high in saturated

fatty acids, particularly palmitate, contribute significantly to the development of insulin resistance. The stress kinases c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) are activated by obesity-associated inflammation, endoplasmic reticulum stress, oxidative stress, and mitochondrial dysfunction, and have been implicated in impaired insulin signaling. **Methods and Results**: We previously demonstrated that palmitate treatment induces insulin resistance in hippocampal and cortical neurons as well as in oligodendrocytes (ODs). In the human oligodendrocyte cell line HOG, palmitate-induced insulin resistance was accompanied by increased levels of phosphorylated JNK (pJNK) and phosphorylated ERK (pERK). Seahorse metabolic analysis further revealed significant mitochondrial dysfunction following palmitate exposure. Extracellular vesicles (EVs) are important mediators of intercellular communication and transport a diverse cargo of RNAs, proteins, and metabolites. MetS has been shown to alter both EV biogenesis and cargo composition. We found that palmitate treatment significantly increased EV release from HOG cells. These palmitate-derived EVs (palEVs) induced insulin resistance and mitochondrial dysfunction in recipient neurons and impaired neurogenesis. Notably, levels of pJNK and pERK were significantly elevated in palEVs compared with control EVs (ctlEVs). Pharmacological inhibition of JNK and ERK during palmitate treatment reduced pJNK and pERK levels in EVs and prevented palEV-induced insulin resistance in recipient neurons. **Conclusions**: Our findings demonstrate that palmitate increases JNK and ERK phosphorylation in both oligodendrocytes and their released EVs. Neurons exposed to palEVs exhibit mitochondrial dysfunction and reduced insulin-stimulated Akt phosphorylation, hallmarks of neuronal insulin resistance. Collectively, these results suggest that EV-mediated transfer of phosphorylated JNK and ERK represents a novel mechanism by which metabolic stress disrupts neuroglial communication, promoting neuronal insulin resistance and mitochondrial dysfunction in the context of MetS.

Disclosures: B. Kim: None. **E.L. Feldman:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.14/Web Only

Topic: C.01. Brain Wellness and Aging

Title: AAV-driven hepatic IL-11 overexpression as a rapid mouse model of aging

Authors: *L. BAI[1], L. ZHANG[2], J. TAN[3];
[1]WuXi AppTec, Shang hai, China; [2]IVPU, [3]WuXi AppTec, Qidong, China

Abstract: Aging is a multifactorial process characterized by progressive loss of physiological integrity, diminished stress resilience, and increased susceptibility to chronic disease. A conserved feature of aging is chronic, low-grade inflammation, or “inflammaging.” Interleukin-11 (IL-11), a member of the IL-6 cytokine family with pro-inflammatory and pro-fibrotic activities, has recently emerged as a regulator of age-related physiology and

pathology; inhibition of IL-11 signaling was shown to extend healthspan and lifespan in mice. Preclinical aging animal models are time- and resource-intensive, limiting throughput for mechanistic studies and drug screening. Here, we evaluate whether sustained, liver-restricted overexpression of mouse IL-11 delivered by adeno-associated virus (AAV) can accelerate aging phenotypes and serve as a rapid model of aging. We used AAV-mediated IL-11 expression to assess systemic and tissue-specific effects on inflammation, fibrosis, metabolic function, and age-related functional decline. Three months after AAV injection, IL-11-overexpressing male mice displayed features resembling accelerated aging, including increased adiposity, metabolic dysfunction, pathogenic signaling, sarcopenia, and higher frailty scores. These findings indicate that liver-targeted IL-11 overexpression may provide a practical platform for mechanistic studies and preclinical testing of interventions addressing age-associated decline.

Disclosures: L. Bai: A. Employment/Salary (full or part-time):; WuXi AppTec. **L. Zhang:** A. Employment/Salary (full or part-time):; WuXi AppTec. **J. Tan:** A. Employment/Salary (full or part-time):; WuXi AppTec.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.15/U16

Topic: C.01. Brain Wellness and Aging

Support: Dorothy Goodwin Scholar Program
UHart College of Arts&Science

Title: Metabolic and circadian effects of dietary modifications in an Alzheimer's Disease mouse model

Authors: P. EDELMAN, *P. SACCHETTI;
Biol., Univ. of Hartford, West Hartford, CT

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memory impairment and cognitive decline, for which no cure currently exists. Although recent pharmacological approaches demonstrate some efficacy in slowing disease progression, their high cost and limited accessibility underline the need for more effective and broadly implementable alternative interventions. Increasing evidence implicates the gut-brain axis as a critical regulator of central nervous system function. Dietary interventions represent a practical approach to influence this axis and are promising adjunctive strategies in AD management. Metabolic therapies, such as the ketogenic diet (KD), have attracted attention due to their ability to shift energy metabolism from glucose to ketone bodies, thus providing an alternative fuel source for peripheral and neural cells. KD has been associated with reduced neuroinflammation and potential attenuation of neurodegenerative processes. Intermittent fasting (IF), defined as time-restricted feeding typically confined to daily intervals of 6-10 hours, represents another

metabolic intervention that induces a physiological state of ketosis through enhanced fatty acid oxidation and ketone body production. Despite its growing popularity, the effects of IF on neurodegeneration and AD-related pathology remain insufficiently characterized. In this study, we compared the effects of KD and IF in the 3xTg-AD mouse model on a C57BL/6 background, alongside wild-type (WT) controls. We investigated diet-induced changes in systemic metabolism, circadian rhythm regulation, and inflammatory pathways, using age and sex as key variables. Metabolic parameters were monitored throughout dietary interventions. Following treatment, hippocampal tissue was collected for gene expression analysis. Our findings reveal diet- and genotype-dependent alterations in metabolic shift and circadian gene expression. Sex-specific differences were observed in metabolic responses across WT and AD cohorts. Collectively, these findings indicate that dietary interventions can substantially influence metabolic and circadian systems, with downstream implications for neuroinflammation and oxidative stress pathways relevant to AD pathogenesis. This work supports further investigation into metabolic therapies as accessible strategies for modifying disease trajectory in AD.

Disclosures: P. Edelman: None. **P. Sacchetti:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.16/U17

Topic: C.01. Brain Wellness and Aging

Title: Nicotinamide Riboside accelerates evidence accumulation during perceptual learning in mice.

Authors: *F. ITURRALDE ROSANO[1], R. OROZCO[2];
[1]Facultad de Quimica, Univ. Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico; [2]Lab. de Cronobiología y Metabolismo, Inst. Nacional de Medicina Genomica, Mexico City, Mexico

Abstract: Background: D-galactose (DGAL) accelerates aging, whereas metformin (MET) and nicotinamide riboside (NR) have geroprotective properties. However, whether these induce beneficial effects on perceptual decision-making remains elusive.Objective: Using computational models to decompose choice behavior, we asked whether MET/NR enhance learning.Methods: Mice were treated with DGAL for 12 weeks; MET and NR were then co-administered while DGAL continued for an additional 8 weeks. Vehicle-treated animals served as the control group. A nocturnal operant 2-AFC task was performed over four consecutive sessions. Decision parameters were obtained by fitting drift-diffusion models (truncated-likelihood and EZ-DDM). In addition, signal-detection d′, win-stay/lose-shift indices, and linear mixed models were computed.Results: A time-dependent increase in learning was observed in the NR group, as reflected by a gradual rise in perceptual sensitivity (d′ 0.59 to1.04; β=0.23, FDR=0.032), a session-dependent gain in drift rate (ρ=0.58, FDR=0.005), lower decision boundaries (FDR=0.041), and progressively fewer omissions together with faster reaction times.Conclusion:

NR strongly enhances learning in a session-driven manner by improving evidence accumulation and engagement, highlighting drift rate as a sensitive cognitive readout for elucidating the effects of geroprotective agents.

Disclosures: F. Iturralde Rosano: None. **R. Orozco:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.17/U18

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01 AG059028-01

Title: Age-related changes to the ultrastructure of myelinated axons and neuroprotective effect of dietary curcumin in the lateral prefrontal cortex layer 3 of the rhesus monkey

Authors: *C. M. FREIRE-COBO[1], M. MEDALLA[2], M. T. VARGHESE[3], N. ZORIA[1], J. I. LUEBKE[4], P. R. HOF[1];
[1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA; [3]George & Anne Ryan Inst. for Neuroscience, Dept. of Biomed. and Pharmaceut. Sci., Univ. of Rhode Island, Kingston, RI; [4]Anat. & Neurobio., Boston Univ., Boston, MA

Abstract: Understanding how aging affects neuronal structure and function is crucial for uncovering mechanisms of synaptic dysfunction and increased vulnerability to age-related cognitive decline. We previously showed changes in the ultrastructure of synapses on pyramidal neurons in area 46 of the dorsolateral prefrontal cortex (DLPFC) in rhesus monkeys across their adult lifespan. Using 3D high-resolution serial block-face scanning electron microscopy, we identified age-related loss of mainly asymmetric axospinous synapses. We showed that curcumin, a turmeric-derived polyphenol with antioxidant and anti-inflammatory effects, helps preserve the morphology of synaptic components and mitochondria in middle-aged (MA) macaques and can delay cognitive decline when used early in the aging process. The impact of structural changes and synapse loss in pyramidal neurons during aging has been extensively studied. However, it remains unclear if changes in myelinated fibers—affecting connections within and between cortical regions—are linked to the reductions in synapse density and dendritic spines. In this study, we expanded our investigation to include age-related ultrastructural changes in myelinated axons across the same brain region and age groups. Our results showed an age-related increase in the percentage of altered myelin fibers (aged: 9%; MA curcumin-treated: 4%; MA control: 5%; young: 1.85%). Observed myelin morphology included sheath splitting and, to a lesser extent, myelin balloons and cytoplasmic inclusions. The g-ratios increased with age, as expected (aged: 0.61; MA curcumin-treated: 0.52; MA control: 0.53; young: 0.46). However, in a thorough comparison of myelinated axon clusters across age groups,

we found distinct aging trajectories for myelin fibers that depended on axon diameter. When examining the morphology of mitochondria within myelinated axons, our results support previous findings on beneficial curcumin's antioxidant effects on dendritic mitochondrial morphology.Overall, our findings suggest that curcumin's properties not only exert beneficial effects on synaptic structure and on both dendritic and axonal mitochondria but could also provide neuroprotective benefits by preserving axonal integrity and preventing myelin degeneration during aging.

Disclosures: C.M. Freire-Cobo: None. **M. Medalla:** None. **M.T. Varghese:** None. **N. Zoria:** None. **J.I. Luebke:** None. **P.R. Hof:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.18/U19

Topic: C.01. Brain Wellness and Aging

Support: R01AG081270-04

Title: Single-cell spatial mapping of mitochondrial homeostasis in aging neurons

Authors: *S. BECK, S. HAN;
Univ. of Florida, Gainesville, FL

Abstract: Single-cell spatial mapping of mitochondrial homeostasis in aging neurons
Neuronal activity is highly energetically demanding, and declining energy maintenance is a core driver of age-related neurodegeneration. Mitochondria are essential for fueling neurons across compartments, including the axon and synapse, and dysregulation of their trafficking, localization, and quality control severely compromises both neuronal function and survival. However, how long-lived, post-mitotic neurons sustain healthy mitochondrial function and metabolic homeostasis throughout an organism's lifespan remains poorly understood. To investigate this, we employed live, single-neuron tracking of mitochondrial physiology in *C. elegans* during aging. We found that aging led to spatially localized metabolic decline. While the soma preserved mitochondrial ATP and reactive oxygen species (ROS) homeostasis, distal and high-energy demanding areas such as neurites and synapses suffered mitochondrial ATP deficits and ROS elevation. Ultimately, these results reveal that aged neurons develop a distinct spatial footprint of metabolic decline, highlighting distal synaptic compartments as critical vulnerabilities during aging.

Disclosures: S. Beck: None. **S. Han:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.19/U20

Topic: C.01. Brain Wellness and Aging

Title: Cell-targeted glucose dendrimer-drug conjugates for healthspan extension through mitochondrial rejuvenation

Authors: *K. MURUGESAN[1], R. GHOSH[1], D. KIM[1], W. LIYANAGE[1], D. CHERUKARAVEEDU[1], D. MOHAVANUR JOTHIVEL[1], S. KANNAN[2], K. PARIKH[1], R. KANNAN[1];
[1]Johns Hopkins Univ., BALTIMORE, MD; [2]Johns Hopkins Univ. SOM, Baltimore, MD

Abstract: Aging across tissues, including the brain, is driven by conserved hallmarks including mitochondrial dysfunction, cellular senescence, and neuroinflammation. Resveratrol (a SIRT1 activator) and rapamycin (a mechanistic target of rapamycin complex [mTORC] inhibitor) extend lifespan across species but have major translational limitations: resveratrol exhibits <1% oral bioavailability, and rapamycin has dose-limiting toxicity. Critically, the nanoscale organization of a therapeutic can govern its intracellular delivery, cell-type selectivity, and physicochemical properties to address these challenges. We engineered glucose dendrimers (GD) conjugated to resveratrol (GD-RV) or rapamycin (GD-Rap) that exploit glucose transporter (GLUT) overexpression in senescent cells, stressed neurons, and activated microglia to achieve cell-selective intracellular delivery. GD-RV synthesized by copper-catalyzed azide-alkyne cycloaddition (7 nm diameter; 15.6 kDa; >95% purity; 6-7 drugs per dendrimer) improved aqueous solubility greater than 600 fold[KP1] over free resveratrol, and cleavable ester linkers conferred pH-responsive release (60±3% at endosomal pH 5.5 vs <12% at pH 7.4 over 48 h; n=3). In hydrogen peroxide-induced senescent human MRC5 fibroblasts, GD-Cy5 co-localized with mitotracker labelled mitochondria (Pearson's r=0.625), confirming GLUT-driven intracellular accumulation[KP2] . GD[KP3] -RV upregulated SIRT1 2.3-fold ($p<0.01$) and restored mitochondrial membrane potential (tetramethylrhodamine ethyl ester staining) while free resveratrol upregulated SIRT1 1.2-fold. In Caenorhabditis elegans (N2; n≥30/group; 3 replicates), GD-RV extended mean lifespan ~15% at a 10-fold lower dose than free drug, with whole-organism fluorescence imaging confirming neuronal localization. Ongoing studies extend the platform to GD-Rap (mTORC1 inhibition, autophagy flux) and assess cognition and neuroinflammation in aging mice models. By improving drug solubility and bioavailability and enhancing the therapeutic index through cell-selective delivery, this novel platform provides a translational route to advance anti-aging therapies, with direct implications for neuronal mitochondrial dysfunction, neuroinflammation, and age-related cognitive decline. Key words: Glucose dendrimer, senescence, SIRT1, longevity, neuroinflammation, resveratrol

Disclosures: K. Murugesan: None. **R. Ghosh:** None. **D. Kim:** None. **W. Liyanage:** None. **D. Cherukaraveedu:** None. **D. Mohavanur Jothivel:** None. **S. Kannan:** None. **K. Parikh:** None. **R. Kannan:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.20/U21

Topic: C.01. Brain Wellness and Aging

Support: NIH R21OD037651
National Institute on Aging R01AG092603

Title: A novel inducible mtDNA mutator mouse to study mitochondrial dysfunction with temporal and spatial control

Authors: *H. M. TOBIAS-WALLINGFORD, S. BARTMAN, L. GASPAR, G. COPPOTELLI, J. M. ROSS;
Univ. of Rhode Island, Kingston, RI

Abstract: Mitochondrial dysfunction is a hallmark of aging and numerous age-related diseases including neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. A wealth of studies supports the accumulation of mitochondrial DNA (mtDNA) mutations as a contributing factor of mitochondrial dysfunction in aging and disease. One of the best models to study the relationship between mtDNA mutations and mitochondrial dysfunction is the mtDNA mutator mouse, which expresses a proofreading-deficient version of mtDNA polymerase-gamma (PolgA), resulting in accelerated accumulation of mtDNA mutations and aging-like mitochondrial dysfunction. Despite its groundbreaking contributions to mitochondrial biology and aging research, this model is limited by the whole-body accumulation of mtDNA mutations, which prevents the investigation of tissue-specific differences in mitochondrial dysfunction. To overcome this limitation, we developed a novel inducible knock-in mtDNA mutator mouse model (iPolgA) that allows spatial and temporal control of mtDNA mutations, enabling the precise study of mitochondrial dysfunction in a tissue- and time-specific manner. Here, we report the generation and validation of this novel model through whole-body induction via Cre recombinase. Our data demonstrate that, upon induction, this model recapitulates the phenotype of the original mtDNA mutator mouse manifesting the same behavioral and biochemical alterations. Additionally, to demonstrate functionality of the novel iPolgA model, we are generating a nervous system-specific mtDNA mutator mouse to evaluate the effects of mitochondrial dysfunction specifically in brain. This work highlights the iPolgA model as a powerful tool for studying the impact of mtDNA mutations on aging and neurodegenerative disorders with enhanced specificity and control

Disclosures: H.M. Tobias-Wallingford: None. **S. Bartman:** None. **L. Gaspar:** None. **G. Coppotelli:** None. **J.M. Ross:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.21/U22

Topic: C.01. Brain Wellness and Aging

Support: R21OD037651
R01AG092603

Title: Mitochondrial Dysfunction Differentially Regulates Glycogen Homeostasis in the Brain and Peripheral Tissues During Aging

Authors: *S. BIBI[1], H. TOBIAS-WALLINGFORD[2], J. M. ROSS[2], G. COPPOTELLI[2];
[1]The Univ. of Rhode Island, Kingston, RI; [2]Univ. of Rhode Island, Kingston, RI

Abstract: Mitochondrial dysfunction is a fundamental hallmark of aging and has been implicated in the development of numerous age-associated disorders, including neurodegeneration and sarcopenia. Altered glycogen metabolism has also emerged as a feature of aging, with glycogen accumulation reported in several cell types within the aging brain, particularly astrocytes and neurons. Based on these observations, we initially hypothesized that mitochondrial dysfunction would promote glycogen accumulation in the brain. To test this hypothesis, we examined glycogen content in the mtDNA mutator ($Polg^{AD257A/D257A}$) mouse, a well-established model of accelerated aging caused by the progressive accumulation of mitochondrial DNA mutations, to investigate whether mitochondrial dysfunction promotes glycogen accumulation in brain and peripheral tissues. Surprisingly, histological analyses using Periodic Acid-Schiff (PAS) and diastase-PAS (dPAS) staining, together with colorimetric glycogen quantification, revealed that mitochondrial dysfunction promotes the accumulation of free glycogen in skeletal muscle and cardiac tissue, but not in the brain or other examined tissues. Proteomic analyses further identified dysregulation of multiple proteins involved in glycogen metabolism, suggesting that mitochondrial dysfunction disrupts glycogen processing in metabolically active tissues. We propose that this aberrant glycogen accumulation may impair contractile and metabolic function, thereby contributing to the development of sarcopenia. Future studies will investigate the mechanistic relationship between glycogen accumulation and muscle decline using a muscle-specific model of mitochondrial dysfunction and determine whether interventions such as exercise can mitigate these effects by enhancing oxidative metabolism and improving glycogen utilization. Collectively, our findings identify disrupted glycogen metabolism as a previously unrecognized biochemical signature of mitochondrial dysfunction that may link impaired mitochondrial homeostasis to systemic aging and age-related muscle decline.

Disclosures: S. Bibi: None. **H. Tobias-Wallingford:** None. **J.M. Ross:** None. **G. Coppotelli:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.22/U23

Topic: C.01. Brain Wellness and Aging

Support: P51OD01110
R24AG07313
3RF1NS121913-S1
P50AG047366
P30AG066515
P30AG072947
R24AG073199
R01AG087945
P30AG066514
K25AG086663
A25-0261

Title: Proteomic profiling of aging rhesus macaque biofluids reveals conserved neurosenescence and structured late-life heterogeneity

Authors: *G. B. DINIZ[1], K. SCHWARTZ[1], C. ERICES[1], S. P. OTT[1], D. J. GRIGGS[1], C. L. SUTPHEN[2], J. H. MENDIOLA[3], D. BECKMAN[1], P. R. HOF[4], E. N. WILSON, Jr.[3], J. H. MORRISON[1];
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Abstract: Aging is the primary risk factor for neurodegenerative disease, yet the molecular architecture of physiological brain aging remains incompletely defined in translational models. To characterize age-associated proteomic remodeling across central and peripheral compartments, we profiled cerebrospinal fluid (CSF) and plasma from 66 rhesus macaques (Macaca mulatta; 5.9-33.6 years) using the NULISAseq CNS Disease Panel and benchmarked findings against human reference samples. Proteomic remodeling was substantially broader in plasma than in CSF. Approximately 38% of plasma proteins exhibited significant age associations, compared to 19% in CSF. Canonical neurosenescence markers demonstrated conserved age-dependent modulation across primates. Neurofilament light (NEFL), neurofilament heavy (NEFH), glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (CHI3L1), chitinase-1 (CHIT1), and triggering receptor expressed on myeloid cells 2 (TREM2) increased with advancing age, indicating coordinated neuronal, astrocytic, and microglial remodeling. In contrast, several synaptic-associated proteins exhibited age-related decline. Members of the neuronal pentraxin family (NPTX1, NPTX2, and NPTXR) decreased selectively in CSF and were positively associated with the neurotrophic factor pleiotrophin (PTN), suggesting coordinated remodeling of synaptic maintenance pathways during aging. Aging was also accompanied by compartment-specific changes in inflammatory and metabolic stress proteins, including IL6, IL18, CCL2, and GDF15, consistent with conserved inflammaging signatures. Beyond directional changes in protein abundance, aging was associated with progressively increased inter-individual proteomic heterogeneity. Unsupervised clustering

revealed reproducible molecular subgroups within geriatric animals, particularly in CSF, that were not fully explained by chronological age. These states were characterized by coordinated differences in barrier-associated proteins, neuronal pentraxins, immune mediators, and amyloid- and tau-related analytes. Together, these findings demonstrate that aging in rhesus macaques is characterized by conserved neurosenescence signatures, selective synaptic remodeling, and the emergence of structured late-life molecular heterogeneity. The resulting dataset establishes a translational framework for aligning non-human primate aging studies with human biomarker paradigms and provides a foundation for investigating early molecular events that precede overt neurodegeneration.

Disclosures: G.B. Diniz: None. **K. Schwartz:** None. **C. Erices:** None. **S.P. Ott:** None. **D.J. Griggs:** None. **C.L. Sutphen:** None. **J.H. Mendiola:** None. **D. Beckman:** None. **P.R. Hof:** None. **E.N. Wilson:** None. **J.H. Morrison:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.23/U24

Topic: C.01. Brain Wellness and Aging

Support: 5T32NS045540-22
5R01AG076835-05

Title: Investigating the interface between epigenetic and metabolism underlying memory formation in the adult and aging brain

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Abstract: Emerging evidence indicates that there are chromatin modifications that decrease accessibility of memory-associated genes, resulting in dysfunction of synaptic plasticity that occurs as we age and is exacerbated in the context of Alzheimer's disease (AD). The dysregulation of the epigenome may occur due to transcriptional regulators and metabolic enzymes becoming uncoordinated in the aging brain, though the molecular mechanisms linking metabolic state to chromatin accessibility during memory processes remain poorly understood. In recently published work, the Wood lab has identified the transcriptional regulator Calcium Responsive Transactivator (CREST) as a potential keystone coordinator of epigenetic and metabolic mechanisms necessary for memory processes, making it a point of vulnerability in age-associated epigenetic malfunction. Genomic analyses revealed that *Crest* expression decreases in human AD-affected brain tissue, and altered *Crest* expression correlates with longitudinal changes in AD pathology. CREST levels also correlate with age-associated memory deficits, showing declines across the mouse lifespan in the hippocampus and in AD model mice.

Our published data showed that manipulating CREST bidirectionally, including via Y397 phosphorylation-site point mutations, affects synaptic plasticity and long-term memory. Preliminary data suggest that CREST may orchestrate the regulation of acetyl-CoA levels via binding to the competing acetyl-CoA regulatory enzymes *Acss2* (increases acetyl-CoA) and *Acc1* (decreases acetyl-CoA by converting it to malonyl-CoA). Acetyl-CoA is a necessary component in histone acetylation, which itself is reduced in the aging brain, suggesting that Acc1 dysregulation may contribute to the histone hypoacetylation observed at memory-associated loci with age. We have since investigated the relationship between CREST and ACC1 through targeted manipulations paired with both the Object Location Memory (OLM) task and the Objects Updating Location (OUL) task. The OUL task builds on the OLM by examining memory updating, a process that specifically becomes impaired with aging: aged (18-month) C57Bl/6 mice exhibit severe impairment in memory updating even when long-term memory formation remains intact. Importantly, inhibition of ACC1 in the dorsal hippocampus appears to alleviate these age-related memory updating deficits, suggesting ACC1 may represent a functionally relevant downstream target. Therefore, CREST interactions with ACC1 appear as a potential key point of vulnerability in the dyscoordination of epigenetic mechanisms implicated in age-associated cognitive decline.

Disclosures: J.A. Picone: None. **T.L. Fetterly:** None. **D. Matheos:** None. **M.A. Wood:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.24/U25

Topic: C.01. Brain Wellness and Aging

Support: NIH NINDS, R01 NS119605
US Army/ARL W911NF2310145

Title: Loss of endothelial Caveolin-1 accelerates the aging process of the threat response

Authors: *E. KORZUS[1], K. SHULER[1], J. STEINHAUSER[1], J. YAN[2], D. V. AGOSTON[3], J. BADAUT[4], A. OBENAUS[2];
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Abstract: Although biological and cognitive brain aging are innate processes, they are generally undesirable, and accelerated aging poses significant societal, economic, and personal concerns. One quantifiable indicator of neurological issues is neurovascular uncoupling, which hampers bidirectional communication between neurons and their supplying blood vessels. Caveolin-1 gene (Cav-1), expressed in endothelial cells of blood vessels, contributes to neurovascular coupling. We report that disruption of Cav-1 function within endothelial cells (EC-Cav1-KO)

results in increased responses to both learned and unlearned threats in young adult brains, a phenomenon typically associated with aging brains. Specifically, loss of Cav-1 in endothelial cells impairs the subsiding of learned threat responses and contributes to aging-related increases in relapse into threat response. In summary, the findings regarding threat extinction indicate that young adult EC-Cav1-KO mice exhibit modulation of learned threat responses comparable to that of old wild-type mice. Conversely, relapse into threat recognition is more pronounced in aged EC-Cav1-KO mice. This indicates that Cav-1 influences the rate of brain aging and abnormality in the threat response. While further evaluation is necessary to confirm translational relevance, these studies provide evidence that Cav1 regulation of neurovascular coupling may serve as a robust predictor of accelerated aging of emotional regulation and, by extension, of age-related brain vulnerability.

Disclosures: E. Korzus: None. **K. Shuler:** None. **J. Steinhauser:** None. **J. Yan:** None. **D.V. Agoston:** None. **J. Badaut:** None. **A. Obenaus:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.25/U26

Topic: C.01. Brain Wellness and Aging

Support: NIH NIAAA AA031376 - H.N. Richardson
UMass IALS Midigrant - H.N. Richardson
UMass CNS Seed-Bridge funding - H.N.Richardson

Title: Baseline novel object preference predicts total alcohol intake in middle aged female mice

Authors: *M. SCHMITT[1], A. SINHA[3], S. HAZEN[3], T. GAHLOT[3], Z. TIGHIOUART[3], A. HAN[2], A. MILCZAREK[3], G.-E. GRAHAM[4], H. N. RICHARDSON[4];
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Abstract: In 2024, nearly a quarter of U.S. middle-aged adults reported a binge drinking episode within the last month. While aging is the largest risk factor for dementia, alcohol use can accelerate the effects of aging, increasing the risk of early cognitive decline and damage to myelinated white matter fiber tracks. This highlights the importance of understanding the mechanisms linking binge drinking, cognitive abilities, and myelin health in this aging population. To begin dissecting these relationships in middle-aged mice, we tested spatial and recognition memory before and after alcohol drinking starting at 11 months of age using a conditional double-transgenic myelination reporter mouse line (NG2-CreER^{TM}/Tau-mGFP). Using the drinking-in-the-dark (DID) binge drinking model, male and female mice were singly housed and given 4 weekly cycles of intermittent access to unsweetened 20% v/v alcohol or

water (n=8-9/group/sex). Each weekly DID cycle consisted of three days of 2 hours of drinking per day followed by one "binge" day of 4 hours of drinking. Post-drinking memory testing was conducted one week following the last DID cycle. Middle-aged mice exhibited binge-like drinking and escalated alcohol intake similar to that observed with the DID model in adolescents and younger adults. Alcohol drinking increased across the four DID cycles in males and females, with sex differences noted in the patterns of drinking and amount of alcohol consumed. Binge day drinking escalated earlier in females and by the 4th cycle, females binge drank significantly more than males. We also found sex differences in cognitive readouts and their relationship with alcohol drinking. Female preference for novel objects during the baseline (pre-alcohol) short-term recognition memory task was predictive of how much total alcohol they consumed over the four-week drinking period. These findings show that with intermittent access, middle-aged mice binge drink alcohol, with escalated intake more pronounced in females, and higher novelty preference predictive of total intake in females. This study will address an important gap in how binge drinking affects cognitive processes later in life. Additionally, leveraging the double-transgenic myelination reporter mouse line will allow us to identify how binge drinking affects myelin production in aging populations.

Disclosures: M. Schmitt: None. **A. Sinha:** None. **S. Hazen:** None. **T. Gahlot:** None. **Z. Tighiouart:** None. **A. Han:** None. **A. Milczarek:** None. **G. Graham:** None. **H.N. Richardson:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.26/U27

Topic: C.01. Brain Wellness and Aging

Support: NIH NIAAA AA031376
UMass IALS Midigrant
UMass CNS Seed-Bridge Funds

Title: Voluntary alcohol drinking corresponds with alterations in oligodendrocyte lineage populations in the cingulum bundle of aged female mice

Authors: *Z. TIGHIOUART[1], M. SCHMITT[2], G.-E. GRAHAM[1], H. N. RICHARDSON[1]; [1]Psychological and Brain Sci., [2]Neurosci. and Behavioral Grad. Program, Univ. of Massachusetts Amherst, Amherst, MA

Abstract: Chronic heavy drinking and alcohol use disorder (AUD) cause damage to brain regions implicated in stress regulation and relapse vulnerability, including the medial prefrontal cortex (mPFC), hippocampus, and amygdala. The cingulum bundle is a large white matter tract connecting these regions. The health of axons within this tract depends on myelin sheaths formed and maintained by oligodendrocytes (OLs). Thus, disruption to cellular dynamics could alter the

fate of OL lineage cells from the proliferating stage through differentiation and maturation of OLs, ultimately leading to myelin loss and circuit dysfunction. Previous studies show the cingulum is structurally and functionally impaired with AUD, consistent with disrupted myelination. To investigate the mechanisms underlying the effects of alcohol on the cingulum bundle, we used a double transgenic reporter mouse line to test how binge drinking impacts OL lineage transition during aging. This transgenic line allows for temporally controlled cell-specific labeling of PDGFRα+ OL progenitors following tamoxifen-induced recombination, allowing for tracking of OL lineage cells across their developmental stages. Seventeen-month-old female Pdgfrα-CreER^{TM}-eYFP mice were injected with tamoxifen to induce Cre-recombination, followed by 10 weeks of voluntary alcohol (unsweetened 20% v/v) or water (n=6/group). Brains were processed for immunofluorescent labeling of oligodendroglial lineage cells using a combination of markers, followed by confocal imaging. Images were analyzed using Nikon NIS Elements software. Using anatomical landmarks, the full anterior-to-posterior extent of the cingulum bundle was captured to include the mPFC, diagonal band of Broca, hippocampus, and ventral tegmental area. Cells that contained the PDGFRα+ signal were identified as OL progenitors, while cells that contained aspartoacylase (ASPA), an enzyme that is highly expressed late in maturation, were identified as myelinating OLs. We investigated for relationships between alcohol consumption and the density of OL progenitors and myelinating OLs. Total voluntary alcohol consumption was positively correlated with OPC density within the cingulum bundle in the region containing the mPFC. YFP-labeled cell analyses are being used to delineate the proliferating phase from cellular differentiation and maturational phases to test for a shift in cellular dynamics and further elucidate the cellular mechanisms. Overall, these findings link cellular pathology to prefrontal cingulum bundle tracts and help establish a mechanistic framework for understanding how alcohol remodels brain networks in the aging brain.

Disclosures: Z. Tighiouart: None. **M. Schmitt:** None. **G. Graham:** None. **H.N. Richardson:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.27/U28

Topic: C.01. Brain Wellness and Aging

Support: R01 AG003376
F32 AG033460
McKnight Brain Research Foundation
HHMI 5200006942

Title: Age-related differences in behavior-driven cell activity occur in lateral but not medial entorhinal cortex

Authors: J. P. LISTER[1], A. E. COMRIE[2], *C. A. BARNES[3];
[1]Dept. of Pathology and Lab. Med., David Geffen Sch. of Med. UCLA, Los Angeles, CA; [2]Mechanistic Cognitive Neurosci., HHMI Janelia Res. Campus, Ashburn, VA; [3]Univ. of Arizona, Tucson, AZ

Abstract: The hippocampus integrates spatial information from medial entorhinal cortex (MEC) with non-spatial, sensory information from lateral entorhinal cortex (LEC) to form episodic memories. Age-related changes in the hippocampus (HPC) have been reported and linked to memory dysfunction, but little is known about how aging affects the entorhinal inputs to HPC. MEC and LEC population activity was investigated in adult vs. aged rats (n=48) by quantifying the expression of the immediate early gene *Arc* across two track-running behavioral sessions with odor cues. The behavioral sessions occurred in a constant spatial environment with distinct visual cues on all four walls; these conditions were chosen to consistently reactivate the same populations of MEC "grid" and other spatially sensitive cells. Odorant cues were also placed along the track path to potentially engage LEC neuronal populations. There were two behavioral groups; the AA behavior group was exposed to the same sets of odorants during both sessions, whereas the AB group encountered a distinct set of odors during the second session compared to the first. *Arc* localization to distinct cellular compartments allows the determination of the behavioral epoch in which the cell was active (if active in behavior session 1, *Arc* is present in the cytoplasm; if active in session 2, *Arc* is present in the nucleus), and expression was visualized via fluorescence *in situ* hybridization. We used Generalized Linear Models to assess effects of behavior, age, and other factors on neuronal activation, and we found that aging did not affect the percentage of neurons active in MEC or their patterns of *Arc* expression across sessions, consistent with a circuit that reflects stable representations of repeated spatial experiences. Fewer cells, however, were activated in LEC of aged rats following behavior ($p<0.05$), indicating this region is selectively hypoactive as a function of aging. Furthermore, in both age groups, more total LEC neurons were activated during the second behavioral session compared to the first ($p<0.05$). This may reflect increasing engagement of temporally responsive LEC neurons as reported in electrophysiological studies. Taken together, these data: 1) suggest that behavior-driven LEC cell activity is selectively vulnerable during aging, while cells in MEC navigation circuits remain relatively resilient to the impact of aging; and 2) are consistent with the hypothesis that both adult and aged LEC may provide a temporal tag for episodic memories in downstream HPC.

Disclosures: J.P. Lister: None. **A.E. Comrie:** None. **C.A. Barnes:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.28/U29

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant RF1 AG081767
McKnight Brain Research Foundation

Title: Aging decreases coupling of spatially tuned mPFC-HC neurons in spatial decision making

Authors: *S. SRIVATHSA[1], C. STERZINAR[1], M. SPONSELLER[1], V. M. GARZA[2], E. R. CHURCH[3], M. WARRIER[1], S. L. COWEN[4], C. A. BARNES[5];
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Abstract: Spatial decision-making requires animals to integrate spatial context, recent experience and rewards to guide choices. Flexible decision-making is altered with age, but the underlying changes to hippocampal (HC) and medial-prefrontal cortical (mPFC) neurons that support spatial decision-making remain unclear. Neurons in the intermediate (iHC) and ventral (vHC) hippocampus regions project directly to prelimbic (PL) and infralimbic (IL) cortices of the mPFC, providing a pathway for interactions between these regions. To examine how HC-mPFC activity change with age, we trained young (n=8) and old (n=8) male F344 rats on a spatial alternation task. Old rats showed reduced performance on the spatial working memory component of the task, even after 21 training sessions. Following acquisition, rats were implanted with dual-bundle hyperdrives targeting CA1 and CA3 regions of the iHC and vHC, as well as PL and IL regions of the mPFC. Neural activity was recorded simultaneously from these regions for an additional 13 to 21 sessions, during which old rats continued to show spatial working-memory impairments. Consistent with dorsal HC, place cell peak firing rate, place field size, and spatial sparsity did not differ between age groups (Crown et al., 2022). Spatial information-per-spike was increased in the vHC of old rats, similar to dHC. Spatially tuned mPFC neurons showed similar properties between age groups, except for lower peak firing rates selectively in the IL region of aged rats. The fraction of spatially selective mPFC cells showing bidirectional firing was also lower in aged rats than in young. We observed significant pairwise correlations between ivHC and mPFC spatially tuned neurons in young and old rats on the spatial working memory component of the task. When we examined pairwise correlations pre- and post-choice, young rats showed increased HC-mPFC correlations pre-choice. Old rats did not show this effect. It is possible that the higher ivHC-mPFC pre-choice correlation in the young rats facilitate decision-making. The lack of this correlation may contribute to the worse spatial working-memory performance in old rats.

Disclosures: S. Srivathsa: None. **C. Sterzinar:** None. **M. Sponseller:** None. **V.M. Garza:** None. **E.R. Church:** None. **M. Warrier:** None. **S.L. Cowen:** None. **C.A. Barnes:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.29/U30

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant RF1 AG081767
McKnight Brain Research Foundation

Title: Reduced vHC-mPFC theta synchrony and elevated mPFC delta power accompany spatial working-memory impairment in aged rats

Authors: *C. STERZINAR[1], S. SRIVATHSA[2], M. SPONSELLER[3], V. M. GARZA[4], E. R. CHURCH[5], M. WARRIER[3], S. L. COWEN[6], C. A. BARNES[7];
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Abstract: Coordination between the medial prefrontal cortex (mPFC) and hippocampus (HC) is essential for spatial decision-making, a process affected by age. Communication between these structures is thought to be facilitated by low frequency oscillations including theta (6-12Hz) and delta (0.5-4Hz). Theta occurs in the HC during locomotion. In the mPFC both theta and delta are present during periods of elevated working-memory demand. Increased HC-mPFC theta synchrony during decision-making correlates with more accurate performance. It is unknown how theta synchrony varies between hippocampus (intermediate (iHC) and ventral (vHC)) and mPFC subregions (prelimbic (PL) and infralimbic (IL)), and how it is impacted by age. We trained young (n=8) and old (n=8) male F344 rats on a spatial alternation task and observed persistent lower performance accuracy in old rats on the spatial working-memory component. Following acquisition, local field potential recordings were collected for 13-21 sessions from both HC and mPFC subregions. Because young rats generally moved at higher speeds compared to old rats on both correct and incorrect trials, we only compared frequency, power, and coherence measures on trials where speed was matched between age groups. Robust theta activity was observed in the iHC and vHC in both age groups during locomotion, with no differences in power or frequency. In contrast, mPFC theta power during locomotion was lower in old rats than in young, whereas mPFC delta power was greater in old rats. HC-mPFC theta coherence was increased before choice on correct spatial working memory trials compared with incorrect trials in young rats, whereas old rats showed no coherence difference between correct and incorrect trials. The increase in coherence prior to correct choices in young rats was particularly pronounced between vHC and IL and PL regions. The lower vHC-mPFC theta synchrony prior to the choice point in old rats may contribute to age-related differences in spatial working memory accuracy. Given that mPFC delta activity has been implicated in working-memory and reward processing, the elevated mPFC delta power in old rats may reflect an alternate state that affects HC-mPFC coordination during spatial decision-making.

Disclosures: C. Sterzinar: None. **S. Srivathsa:** None. **M. Sponseller:** None. **V.M. Garza:** None. **E.R. Church:** None. **M. Warrier:** None. **S.L. Cowen:** None. **C.A. Barnes:** None.

Poster

PSTR219: Metabolic and Neural Changes Across Brain Aging: Experimental Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR219.30/U31

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 5R01 AG072643
McKnight Brain Research Foundation

Title: Lifespan assessment of spatial reference memory performance in TgF344-AD rats: strategy use across learning in AD rats.

Authors: *M. A. ZEMPARE[1], C. STERZINAR[2], M. SPONSELLER[1], S. SRIVATHSA[3], S. L. COWEN[4], P. F. WORLEY[6], C. A. BARNES[5];
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Abstract: Alzheimer's disease (AD) is characterized by progressive impairments in hippocampal-dependent learning and memory. The present study examined the emergence of spatial cognitive memory deficits across aging in transgenic Fischer 344 AD (TgF344-AD) and wild type (WT) control rats using the Morris watermaze (MWM) task. A cross-sectional design was employed in which performance on this task was examined in male rats. We have completed data collection in rats aged 4, 5, 6, 7, 8, 9, 10, 11, 12, and 15-16 and 20-21 months (n=158). Here, we report spatial reference memory performance and strategy utilization in the male rats across 4 days of testing (6 trials/day). No differences in spatial memory performance were observed between AD rats and their age-matched controls from 4-12 months of age. While WT rats at 15-21months are worse at learning the spatial task compared to the younger rats, AD rats of this age are significantly worse compared to their WT age matched counterparts across all days of training. We also characterized the swimming trajectories of rats across learning to see if there were differences in the strategies used by WT and AD rats. A preference for specific strategies may reflect the progressive impact of emerging pathology on the brain. Using Rtrack, a strategy classifier(Overall et al., 2020), the use of hippocampal-dependent allocentric strategies was significantly less in 15-21-month AD rats than their WT counterparts. While the lower allocentric strategy use was particularly striking on the final day of learning (Day 4), the reduced allocentric strategy use was apparent as early as 6 months of age in the AD rats. This implicates dysfunction of the hippocampus and other temporal lobe regions. The older AD rats used platform independent strategies (thigmotaxis and random path) most throughout training, with procedural strategies being comparable between WT and AD rats across the first three days of learning. The heavy reliance on the use of platform independent strategies by aged AD rats suggests that these rats may be using parallel striatal navigation circuits for task solution. This may indicate that these parallel circuits are relatively unaffected by the AD pathology in this model.

Disclosures: M.A. Zempare: None. **C. Sterzinar:** None. **M. Sponseller:** None. **S. Srivathsa:** None. **S.L. Cowen:** None. **P.F. Worley:** None. **C.A. Barnes:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.01/U32

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

Support: National Institute of Aging R21AG075024
Roddy Foundation

Title: Gene-edited HTRA1 mutant rats show behavioral, vascular, and molecular features of Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL)

Authors: *B. MONTE[1], J. DAVIS[2], X. ZHU[3], F. XU[2], M. MAJCHRZAK[2], M. CABRAL[2], W. M. VAN NOSTRAND[2], B. HEALEY[2], S. KOUNDAL[5,6], J. K. ROBINSON[2], H. BENVENISTE[7], W. E. VAN NOSTRAND[4];
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Abstract: Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL) is a hereditary cerebral small vessel disease (CSVD) caused by mutations in the High Temperature Requirement A1 (HTRA1) serine protease. While previous CARASIL mouse models have reproduced some features of the disease, they have not fully recapitulated the pathogenesis observed in human CARASIL. To address this gap and provide a more clinically relevant model, we generated a gene-edited rat model harboring the loss-of-function HTRA1 mutation p.R302Q, designated CRHTRA1. At 12 months (M) of age, CRHTRA1 rats exhibit impaired spatial working memory in the radial arm maze and marked gait disturbances measured by Catwalk XT, as well as significant thickening of pial and parenchymal cerebral vessel walls with concomitant reductions in lumen area compared to WT controls. Reductions in vascular smooth muscle actin and increases in vascular extracellular matrix (ECM) proteins were present in CRHTRA1 rats, consistent with reports of CARASIL. Analysis of Fractional Anisotropy, a measure of white matter integrity obtained using Diffusion Tensor Imaging, revealed microstructural changes in CRHTRA1 white matter that overlapped with regions showing atherosclerotic changes. Whole brain RNA sequencing of both groups identified 1,313 differentially expressed genes after false discovery rate adjustment, with subsequent pathway analysis revealing upregulation of signaling pathways associated with HTRA1 catalytic dysfunction and ECM remodeling in CRHTRA1 rats. To further elucidate the mechanisms underlying vascular pathology in CRHTRA1 rats, proteomic analysis was conducted on cerebral vessel-enriched samples, identifying 324 differentially expressed proteins categorized as vascular, mitochondrial, and respirasome-associated. Proteins associated with vascular endothelium maintenance and adherens junctions were among those differentially expressed in CRHTRA1 rats and were also present in neuroinflammatory and immune system activation pathways. Mitochondrial and respirasome proteins were involved in oxidative phosphorylation

and mitochondrial dysfunction pathways. These findings contribute to our understanding of CARASIL HTRA1 mutations and their impact on CSVD development.

Disclosures: B. Monte: None. **W.E. Van Nostrand:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.02/V1

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

Support: National Science Foundation HSI-STEM Award #1953448.
NIH R15N5095317
Daisy Brand Undergraduate Research Grant

Title: UBR5's Role in TDP34 Fragment Recognition

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Abstract: In many neurodegenerative diseases, the human Tar DNA-binding Protein 43 (TDP43) is proteolytically cleaved into shorter fragments that can misfold, oligomerize, and form toxic aggregates within cells. Our lab has shown that cells employ multiple, overlapping protein quality control pathways to recognize and eliminate these fragments before they accumulate. In this study, we investigate the role of the E3 ubiquitin ligase N-Recognin 5 (UBR5) in the clearance of TDP43 fragments. Although UBR5 is classically known to recognize protein fragments bearing N-terminal basic residues such as arginine, we discovered that it recognizes proteolytic TDP43 fragments through a broader mechanism. We propose that UBR5 engages previously ubiquitylated TDP43 fragments and acts as a ubiquitin chain elongator to signal their destruction. To examine this, we began by using site-directed mutagenesis to create a lysine-lacking version of a specific disease-associated fragment of TDP43 to prevent its ubiquitylation. We are now using these constructs to define the molecular basis by which UBR5 recognizes and targets toxic TDP43 fragments for degradation.

Disclosures: A.G. Pellacani: None. **O. Van:** None. **W.M. Mirembe:** None. **C.S. Brower:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.03/V2

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

Title: Multiscale HD-MEA profiling reveals early hyperexcitability and axonal dysfunction in a human iPSC-derived GRN-FTD model

Authors: *M. HRUSKA-PLOCHAN, F. GALLUZZI, E. GUELLA, P. MANOGARAN; MaxWell Biosystems, Zurich, Switzerland

Abstract: Heterozygous loss-of-function (LOF) mutations in the granulin precursor gene (GRN) are a major genetic cause of frontotemporal dementia (FTD), leading to GRN haploinsufficiency. Reduced neuronal progranulin impairs lysosomal function and proteostasis, promoting synaptic dysfunction and TDP-43 pathology, contributing to altered functional connectivity and selective neuronal vulnerability. Human iPSC-derived models of GRN haploinsufficiency are valuable tools for disease phenotyping and therapeutic discovery; however, translating these models into disease-relevant functional endpoints remains challenging. Using the MaxTwo High-Density Microelectrode Array (HD-MEA) multiwell platform (MaxWell Biosystems, 26,400 electrodes per well), which enables non-invasive, label-free, real-time electrophysiological recordings, we longitudinally profiled functional phenotypes in a human iPSC-derived FTD model across network, cellular, and axonal scales. iCell Induced Excitatory Neurons were co-cultured with normal iCell Astrocytes 2.0 and compared between an Apparently Healthy Normal (AHN) control line and an isogenic line carrying a heterozygous GRN R493X LOF mutation. Spontaneous activity was monitored from DIV 6-50. MaxWell's ActivityScan and Network assays detected reproducible disease-associated changes across replicates and timepoints, with significantly elevated firing rates and reduced inter-spike intervals emerging by DIV 15. These early abnormalities indicate that HD-MEAs capture disease-related dysfunction before overt structural degeneration. GRN mutant cultures also showed significantly altered network synchrony, including more frequent and robust network bursts, shorter inter-burst intervals, and prolonged bursting, supporting a hyperexcitable network phenotype. MaxWell's AxonTracking Assay reconstructed action potential propagation along individual axonal arbors. GRN mutant neurons displayed reduced axonal branching and shorter neurites, extending the disease-associated phenotype from early network and single-cell alterations to axonal architecture. Together, these data identify an early, reproducible, multiscale, and multiparametric electrophysiological signature of GRN haploinsufficiency in a human iPSC-derived FTD neuronal model, longitudinally captured on a single HD-MEA platform with scalable assay workflows. This approach links network-level dysfunction with single-cell and axonal phenotypes, providing robust functional endpoints for therapeutic window definition, progression monitoring, and future therapy-response studies in human neurodegeneration models.

Disclosures: M. Hruska-Plochan: None. **F. Galluzzi:** None. **E. Guella:** None. **P. Manogaran:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.04/V3

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

Support: NIH Grant R01AG081379
Rutgers start-up fund

Title: Enhancing neuronal glucose metabolism restores energy homeostasis and improves survival in MAPT-related frontotemporal dementia models

Authors: *Y. TONG[1], C. MANSOUR[1], A. KENNY[1], M. RAJMOHAMED[1], E. CHILES[2], B. ABID[1], A. NAKHLA[1], X. SU[2,3], C. WONG[1];
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Abstract: Glucose is the primary energy source supporting the high metabolic demands of brain cells. Reduced cerebral glucose uptake is a common clinical hallmark of neurodegenerative diseases including frontotemporal dementia (FTD). However, the specific alterations in FTD neuronal glucose metabolism remain poorly understood. MAPT-FTD, a major subtype of FTD, is caused by pathogenic *MAPT* mutations. Here, we demonstrate that enhancing glycolysis rescues neuronal and organismal functions in MAPT-FTD models. Utilizing both *Drosophila* and human induced pluripotent stem cell (iPSC)-derived neurons (iNeurons) expressing MAPT-FTD variants, we identified convergent molecular and metabolic profiles indicative of impaired neuronal glucose oxidation. Specifically, stable isotope tracing metabolomics in $MAPT^{P301L}$ fly brains revealed reduced glycolytic flux in the energy-yielding phase. Furthermore, ATP biosensor imaging demonstrated diminished bioenergetic reliance on glucose in both $MAPT^{P301L}$ fly neurons and $MAPT^{R406W}$ human iNeurons. Upregulating glucose metabolism—either by overexpressing glycolytic enzymes or inhibiting Sirtuin 6 (SIRT6)—effectively restored glucose metabolism in these neurons. SIRT6 inhibition increased the expression of glycolysis-related genes, upregulated glycolytic flux, and promoted glucose-dependent ATP production in both model systems, ultimately improving survival and locomotor activity in $MAPT^{P301L}$ flies. Notably, these metabolic modulations extended the lifespan of flies expressing mutant *MAPT*, but not in those with wild-type *MAPT*, suggesting an allele-specific metabolic vulnerability. Collectively, our findings reveal that impaired glucose oxidation is a central metabolic feature of MAPT-FTD neurons and propose glycolytic enhancement as a potential therapeutic strategy to restore neuronal bioenergetics and ameliorate MAPT-FTD pathology.

Disclosures: Y. Tong: None. **C. Mansour:** None. **A. Kenny:** None. **M. Rajmohamed:** None. **E. Chiles:** None. **B. Abid:** None. **A. Nakhla:** None. **X. Su:** None. **C. Wong:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.05/V4

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

Support: NIH Grant 1R01AG081258-01A1
NIH Grant 1RF1NS132291-01
NIH Grant 1R01AG081874-01
AHA Grant 22TPA970253
AHA Grant 24POST1196128
AHA Grant 25POST1373581
AHA Grant 25CDA1453457

Title: Characterization of neurovascular dysfunction and cognitive impairment in a mouse model of sickle cell disease

Authors: *J. ZACCARELLI MAGALHÃES[1], M. UDO[3], D. J. SMITH[2], J. LANGMAN[1], L. H. MATUGUMA[2], G. NAGAMINE GOMES[1], P. RODRIGUEZ[1], C. T. CITADIN[2], H. LIN[2]; [2]Neurol., [1]UTHealth Houston, Houston, TX; [3]Neurol., Univ. of Texas Hlth. at Houston, Houston, TX

Abstract: Background: Sickle cell disease (SCD) is a hereditary blood disorder caused by a point mutation of the β-globin gene, affecting 306,000 newborns worldwide each year, predominantly among individuals of African heritage. In this disease, hemoglobin polymerizes, causing the cells to assume a rigid sickle-shape. The abnormal hemoglobin does not properly carry enough oxygen through the body leading to serious cardiovascular alterations, including the development of vascular dementia - characterized by cognitive and memory impairment and reduced cerebral perfusion. Although SCD affects both sex, sex-specific differences remain unclear. **Hypothesis**: Middle-aged female and male Townes mice (a mouse model of SCD) have neurovascular dysfunction and cognitive impairment consistent with vascular dementia. **Methods**: Middle-aged female and male Townes and C57BL/6J mice were assessed for functional outcomes (open field, Y-maze, and novel object recognition tests). Cerebrovascular function was assessed via two-photon laser scanning microscopy. Following imaging, cortical and hippocampal tissues were collected for quantification of tight junction proteins. **Results**: Our results indicate that Townes mice of both sexes exhibited: 1) reduced mobility, increased anxiety-like behavior, and impaired memory; 2) neurovascular coupling dysfunction, as evidenced by alterations in red blood cell velocity and microvessel diameter; 3) increased BBB permeability; and 4) decreased tight junction proteins in the cortex and hippocampus. **Conclusion**: Both female and male Townes mice exhibit vascular and behavioral abnormalities consistent with features of vascular dementia, with no detectable sex-specific differences at the functional level. **Acknowledgements**: Funding and support from 1R01AG081258-01A1, 1RF1NS132291-01, 1R01AG081874-01, 22TPA970253, 24POST1196128, 25POST1373581, and 25CDA1453457.

Disclosures: J. Zaccarelli Magalhães: None. **M. Udo:** None. **D.J. Smith:** None. **J. Langman:** None. **L.H. Matuguma:** None. **G. Nagamine Gomes:** None. **P. Rodriguez:** None. **C.T. Citadin:** None. **H. Lin:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.06/V5

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

Support: National Natural Science Foundation of China
Guangdong Basic and Applied Basic Research

Title: Primate-Specific TDP-43 Pathologies Unveiled in Non-Human Primate Models

Authors: *Z. LONGHONG[1], Q. JIA[2], D. LI[5], S.-H. LI[3], X.-J. LI[4], P. YIN[2];
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Abstract: The cytoplasmic mislocalization and nuclear loss of TDP-43 are central pathological features in amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and other neurodegenerative diseases. However, most TDP-43 transgenic mouse models fail to recapitulate these key pathologies, limiting the study of endogenous TDP-43-mediated toxicity. To address this, we turned to non-human primate (NHP) models, which more closely resemble human TDP-43 pathology and gene regulation. We found that primate-specific caspase-4 (CASP4) cleaves TDP-43, generating fragments that translocate from the nucleus to the cytoplasm. Furthermore, mislocalized TDP-43 in monkeys specifically reduces SQSTM1 mRNA stability and suppress PJA1 gene transcription—effects not observed in mouse brains. Additionally, the loss of TDP-43 suppresses transcription of GRINA (Glutamate Ionotropic Receptor NMDA Type Subunit Associated Protein 1) via TDP-43 binding to a primate-specific (CTACCCACA)n motif in exon 1 of the primate GRINA gene—another effect completely absent in mice. Our findings uncover primate-specific pathological events of TDP-43 and provide new insights into TDP-43-associated pathogenesis.

Disclosures: Z. longhong: None. **Q. Jia:** None. **D. li:** None. **S. Li:** None. **X. Li:** None. **P. Yin:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.07/V6

Topic: B.09. Glial Mechanisms

Support: National Key R&D Program of China Grant 2023YFA1800100
Start-up Fund of Guangzhou First People's Hospital to Y.U.L.

Title: In vivo tracking of microglial engulfment of degenerated neurons across temporal scales reveals diurnal rhythmicity

Authors: Z. XIANG[1,2], B. MOU[1,2], M. LI[1,2], L. HUANG[1,2], ***Y. U. LIU**[1,2];
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Abstract: Microglia clear degenerated neurons, but how their phagocytic behavior is dynamically regulated in vivo remains unclear. We performed longitudinal intravital imaging of microglial dynamics in head-fixed, freely behaving mice at subcellular resolution, using a rapid neurodegeneration model induced by cytosolic TDP-43 proteinopathy. Imaging revealed a stereotyped sequence of neuronal degeneration, including reduced firing, nuclear disintegration, soma shrinkage, and fluorescence loss, each accompanied by microglial engulfment. In the absence of microglia, neuronal corpses persisted. High-temporal-resolution imaging identified a stereotyped behavioral sequence of microglial engulfment, termed reach, approach, isolate, and digest (RAID). Behavior-guided Smart-seq further defined distinct transcriptomic states in unactivated, activated non-engulfing, and engulfing microglia. Tracking across day and night phases showed that RAID activity peaked during the day (sleep) phase and was suppressed during the night (awake) phase, accompanied by corresponding shifts in microglial transcriptional states. This pattern was reversed by light-dark cycle inversion and abolished by sleep disruption. Acutely, anesthesia or inhibition of norepinephrine-ADRB2 signaling mimicked the sleep-phase state, whereas ADRB2 activation resembled the awake-phase state. Chronic microglia-specific ADRB2 knockout impaired phagocytosis and increased neuronal corpse accumulation. These results identify day-night regulation as an important determinant of microglial clearance capacity during neurodegeneration.

Disclosures: Z. Xiang: A. Employment/Salary (full or part-time):; Guangzhou First People's Hospital. **B. Mou:** None. **M. Li:** None. **L. Huang:** A. Employment/Salary (full or part-time):; Guangzhou First People's Hospital. **Y.U. Liu:** A. Employment/Salary (full or part-time):; Guangzhou First People's Hospital.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.08/V7

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

Support: NIH Grant R01AG059794
NIH Grant P01 AG019724
NIH Grant P30 AG062422

Title: Distinct reward processing profiles underlying hoarding in behavioral variant frontotemporal dementia and hoarding disorder

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Abstract: Repetitive behaviors, such as hoarding, are one of the core diagnostic features of behavioral variant frontotemporal dementia (bvFTD) and overlap with hoarding disorder (HD). Of patients eventually diagnosed with bvFTD, 50% initially receive a psychiatric diagnosis, including HD, delaying the receipt of appropriate treatment and care planning. Hoarding involves alterations to reward processing, which allow individuals to weigh positive and negative aspects of a stimulus to determine the value or aversion derived from obtaining or discarding it. Though hoarding often occurs in bvFTD, it is unclear if the reward profile and neurobiological mechanisms when the behavior occurs in this context are analogous to those in HD. This study compares the reward deficits underlying hoarding behavior in bvFTD and HD, to improve diagnostic differentiation and inform treatment targets. We recruited 52 patients with bvFTD (20 with hoarding, 32 without), 13 patients with HD, and 24 healthy controls (HC). Consensus diagnosis for HC and bvFTD was determined by multidisciplinary evaluation at the University of California San Francisco Fein Memory and Aging Center while HD participants underwent psychiatric evaluation through the UCSF OCD and Anxiety clinic. Participants completed a series of tasks utilizing pleasant and unpleasant olfactants to probe different aspects of reward processing. Electrodermal activity was collected throughout. We conducted two analyses: in the first, we compared HC, HD, and bvFTD regardless of hoarding status. The results of a mixed effects model showed a significant diagnosis by valence interaction ($\chi^2(2) = 48.18$, $p < .001$) with bvFTD rating unpleasant scents more positively than HC ($p = .012$), and HD rating unpleasant scents more negatively than HC ($p = .022$). Among HD, ratings of unpleasant scents related to Clutter Image Rating scores, such that those with greater bedroom clutter assigned higher ratings to unpleasant scents ($p = .037$). Electrodermal activity in anticipation of pleasant and unpleasant scents revealed a significant diagnosis by valence interaction (χ^2 (2) = 6.97, $p = .031$), with HD showing greater skin conductance response to unpleasant scents ($p = .011$). In the second analysis, comparing bvFTD with and without hoarding, no significant differences emerged in self-report or physiological measures; however, voxel-based morphometry showed hoarding in bvFTD was associated with less atrophy in the left anterior insula. These findings suggest the behavioral manifestations of reward processing deficits in bvFTD and HD are distinct but point to potentially analogous neuroanatomical mechanisms underlying hoarding behavior.

Disclosures: N.G. Cryns: None. **A.R.K. Roy:** None. **M.P. Johnson:** None. **J. Zakrzewski:** None. **V.E. Sturm:** None. **B.L. Miller:** None. **C. Mathews:** None. **D.C. Perry:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.09/V8

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

Support: RO3AG084918

Title: Temporal Changes in Brain Pathology and Gene Expression During the Progression of Chronic Cerebral Hypoperfusion in Female Mice

Authors: *S. LIMAM[1], A. MAZZARELLA[1], R. HERNANDEZ-JIMENEZ[1], A. PATEL[1], A. DHARAP[2];
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Abstract: Chronic cerebral hypoperfusion (CCH) is a major risk factor for neurodegenerative diseases, including vascular dementia. Despite its clinical relevance, the molecular mechanisms underlying the resulting pathology remain poorly understood. Moreover, most mechanistic and preclinical studies have been conducted in male animals, leaving the female brain's molecular responses to CCH largely unexplored. To address this important gap in knowledge, we investigated how CCH affects brain pathology and gene expression in female mice over disease progression, focusing on early (1 month), intermediate (4 months), and long-term (1 year) stages. To induce CCH, female C57BL/6J mice were subjected to the bilateral common carotid artery stenosis (BCAS) model. At each stage, sham and BCAS mice (n=5/group) were evaluated for gross pathology using hematoxylin and eosin staining, white matter integrity using Luxol fast blue staining, glial activation using immunohistochemistry, and neuronal degeneration using Fluoro-Jade C staining. These results showed that, at the early stage of CCH, female mice exhibited mild white matter damage, astrocytic activation, and subtle neuronal degeneration in the cortex and hippocampus. By the intermediate and long-term stages, these pathological changes became more pronounced, with increased white matter damage, glial activation, and neuronal degeneration in both regions. Further, to define the molecular changes associated with CCH progression, genome-wide RNA-seq was performed on hippocampal tissue from sham and BCAS female mice (n=3/group) across all CCH stages. Differential expression analysis was performed using an FDR q-value < 0.05 and FC> 1.5. At the early stage of CCH, 563 genes were differentially expressed in BCAS versus sham mice, including 431 upregulated and 132 downregulated transcripts. In contrast, at the long-term stage, only 31 genes were differentially expressed, including 4 upregulated and 27 downregulated transcripts. Together, these findings provide important insight into the temporal, molecular, cellular, and pathological responses during the progression of CCH-induced injury in the female brain.

Disclosures: S. Limam: None. **A. Mazzarella:** None. **R. Hernandez-Jimenez:** None. **A. Patel:** None. **A. Dharap:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.10/V9

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

Support: NIH Grant 1R21NS139178-01

Title: Probing aggregational effects of heterotypic α-synuclein fibrils in MED using 3D vascularized brain tissue model

Authors: *P. SAHA, J. PAEK;
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Abstract: Multiple Etiology Dementia (MED) is a recently recognized neurodegenerative condition characterized by the co-occurrence of multiple dementias, including Alzheimer's disease, Lewy body dementia (LBD), and Parkinson's Disease Dementia (PDD). A defining pathology of this emerging condition is co-existence of multiple amyloid fibrils in the brain, specifically amyloid-β (Aβ), tau protein, and α-synuclein (α-syn) fibrils. While the pathological consequences of these fibrils have been extensively studied in isolation, little is known about the effect of their interaction on neurodegeneration in MED. This gap persists due to the lack of reliable models to study the pathological effects of heterotypic fibril interactions. To address this issue, we aim to establish a 3D vascularized brain model by co-culturing functional neuronal cells with a self-organized vascular bed to emulate the physiologically-relevant neurovascular unit. Immunofluorescence staining of GAP43, MAP2 and TH indicated matured dopaminergic neuron identity (Fig 1a,b), while perfusion of FITC-dextran (40KDa) solution and CD31 staining demonstrated the perfusable interconnected vascular networks (Fig 1b,c). Using this model, we investigated effects of heterotypic amyloid fibrils on progression of PDD as a model disease of MED. Specifically, we treated our model with various α-syn preformed fibrils (PFFs) in the presence of varying concentrations of Aβ monomers or PFFs and then examined their effects on intraneuronal aggregation which is a defining feature of PDD. Our analysis of puncta-positive cell ratio and intraneuronal α-syn aggregation length confirmed that the distinct α-syn PFF variants induced significantly different aggregation effects, while control groups showed non-detectable aggregation levels. Our future study aims to extend this investigation to a broader spectrum of PDD pathologies, including neuroinflammation, neurodegeneration, and vascular pathologies.

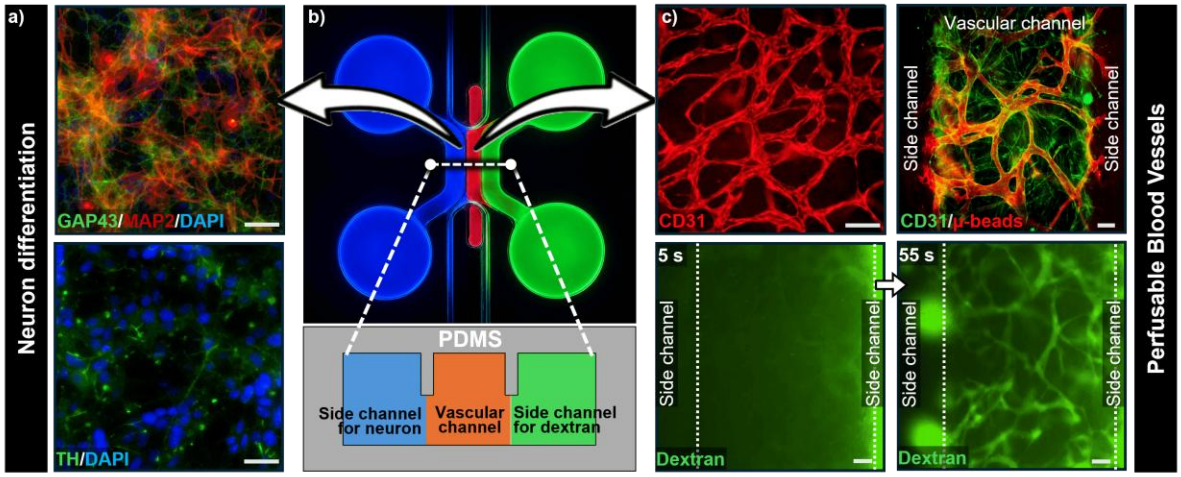


Fig. 1: A microengineered 3D in vitro model of vascularized midbrain tissue. a-c) Characterization of the vascularized midbrain tissue model. One side channel is designated for culturing midbrain dopaminergic neurons, as demonstrated by immunofluorescence staining of GAP43 and MAP2 which confirmed the presence of axonal and dendritic structures, and tyrosine hydroxylase (TH) counterstained with DAPI (blue), validating their dopaminergic identity (a). Scale bars 50 μm. The central vascular channel is used to generate self-organized 3D vascular networks, as confirmed by immunofluorescence staining of CD31. Scale bar 100 μm. Perfusion of red microbeads and FITC-dextran (40 kDa, green) demonstrated the perfusability of the 3D vascular network (c). Scale bars 100 μm.

Disclosures: P. Saha: None. **J. Paek:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.11/V10

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

Support: NIH R35GM146890
T32NS007453

Title: Early glial activation precedes adaptive immune involvement and behavioral decline in a GRN-associated model of frontotemporal dementia

Authors: *K. OSHIMA, I. IFERGAN;
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Abstract: Background: Frontotemporal dementia (FTD) is a leading cause of early-onset dementia, with mutations in the *granulin* (*GRN*) gene representing a major genetic risk factor. *GRN* mutations reduce progranulin (PGRN), a protein critical for lysosomal homeostasis and immune regulation. Increasing evidence implicates immune dysfunction in the pathogenesis of GRN-associated FTD, including glial activation in the CNS and altered inflammatory markers in the blood, serum, and cerebrospinal fluid, suggesting involvement of both central and peripheral

immune compartments. However, the specific immune cell populations and temporal inflammatory changes contributing to disease progression remain poorly defined.
Methods: We used the *GRN*^{R493X} knock-in mouse model, which recapitulates PGRN deficiency observed in FTD, to investigate immune and behavioral changes across disease stages. Male and female *GRN*^{R493X} and wild-type mice were assessed at 3, 6, and 9 months of age using the Elevated Plus Maze, Barnes Maze, and Three Chamber Sociability Test for behavioral changes. Brain and spleen tissues were collected for flow cytometric analysis of immune cell activation and cytokine expression. Immunohistochemistry was used to evaluate glial cell activation and neurodegeneration.
Results: *GRN*^{R493X} mice developed increased risk-taking behavior, and spatial learning and memory deficits by 6 months, followed by impaired social recognition at 9 months. Immune profiling revealed early CNS immune activation, with microglia showing increased CD68, IL-1β, IL-6, and CD86 expression at 3 months, and further increases by 6 months. Astrocytes showed elevated IL-6 levels at 3 months and increased expression of IL-1β, IL-6, and TNF at 6 months. By 6 months, *GRN*^{R493X} mice showed increased accumulation of brain-infiltrating T cells with enhanced expression of activation and effector markers, including CD25, granzyme B, GM-CSF, IFN-γ, and IL-17. Splenic T cells mirrored this pro-inflammatory phenotype, suggesting coordinated peripheral and central immune activation. Histological studies confirmed robust microglial and astrocyte activation in *GRN*^{R493X} brains with increased neurodegeneration as disease progresses.
Conclusion: Our findings suggest that GRN deficiency induces early glial activation followed by peripheral T cell involvement, establishing a chronic inflammatory environment that may drive behavioral deficits in GRN-associated FTD. This work highlights key immune populations and disease stages that may represent therapeutic windows for modulating inflammation in FTD.

Disclosures: K. Oshima: None. **I. Ifergan:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.12/V11

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

Title: ADVANCED NEONATE TREATMENT POSSIBILITIES AND TRANSLATIONAL BIOMARKER EVALUATION AS STRATEGIES FOR EARLY DEVELOPMENT INTERVENTION AND DRUG DEVELOPMENT

Authors: *M. DUDEK[1], **S. KRASSNIG**[1], L. BREZNIK[1], M. DAURER[1], M. PROKESCH[2]; [1]Scantox Neuro GmbH, Grambach, Austria; [2]Discovery, Scantox Neuro, Grambach, Austria

Abstract: ADVANCED NEONATE TREATMENT POSSIBILITIES AND TRANSLATIONAL BIOMARKER EVALUATION AS STRATEGIES FOR EARLY

DEVELOPMENT INTERVENTION AND DRUG DEVELOPMENTStefanie Krassnig, Martin Häring, Balázs Dobrovich, Sara Vušnik, Isabelle Sammer, David Amschl, Stefan Ebner-Benke, Tina Loeffler, Livia Breznik, Magdalena Daurer, Manuela Prokesch*Scantox Neuro GmbH, A-8074, Parkring 12, Grambach, Austria*

Early detection and pre-symptomatic treatment of neurodegenerative diseases have become increasingly significant over the last years. Thus, the early integration of translational biomarkers and subsequent early development intervention in pre-clinical studies is essential for disease prevention strategies. The neurofilament light (Nf-L) protein has emerged as a highly sensitive biomarker to not only track early-stage neurodegeneration but also allowing in-life monitoring of disease progression and therapeutic impact. Elevated levels of Nf-L are reported in lysosomal storage disease, which is also evident in related mouse models including 4L/PS-NA, a model of Gaucher disease, and NPC1−/−, a model of Niemann-Pick disease.To improve therapeutic outcomes and better reflect clinical situations, it is necessary to intervene also in pre-clinical disease settings as early as possible. To address these needs, we established several treatment routes in neonates starting directly at postnatal day 0. Specifically, we can perform not only single but also repeated intraperitoneal, per oral and subcutaneous applications in awake animals on a daily basis. Furthermore, we established intravenous as well as intracerebroventricular injection protocols for neonates to enable fast body- or CNS-related delivery of therapeutic agents, respectively. Importantly, the standardized procedure does not have significant adverse effects on animal survival or development. These approaches are most prominently applied in gene therapy studies using viral constructs (e.g. AAV particles) to modulate the genomic profile during development. However, also early exposure to various types of test compounds can attenuate disease onset and progression.This Poster illustrates our standardized and advanced *in vivo* sampling and surgical techniques, particularly longitudinal Nf-L measurements and neonatal administration routes, which can markedly advance and strengthen preclinical CNS drug development.

Disclosures: M. Dudek: None. **S. Krassnig:** None. **L. Breznik:** None. **M. Daurer:** None. **M. Prokesch:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.13/V12

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

Support: NIA-R01AG8470-01
P20GM148326-01
P30AG072946-03

Title: Induced PAD4 activity worsens hippocampal function and TDP-43 pathology in FTD mice

Authors: *S. LUNDT[1], P. ROCHA-RANGEL[4], J. HUNT[5], D. C. LEE[2], M.-L. B. SELENICA[3]; [2]Sanders-Brown Ctr. on Aging/ Dept. Neurosci., [3]MPP, [1]Univ. of Kentucky, Lexington, KY; [4]Mol. and Cell. Biochem., Sanders Brown Ctr. on Aging, Lexington, KY; [5]Univ. of Kentucky, Sanders Brown Ctr. on Aging, Lexington, KY

Abstract: Alzheimer's disease and related dementias (ADRD) are a group of neurological conditions that result in the loss of many cognitive abilities, including memory loss. More than 6 million individuals in the United States are thought to have some form of dementia with the number expected to rise given the large aging population in the country. Importantly, TDP-43 is a driving factor or co-pathology in many. TDP-43 undergoes many post-translational modifications (PTMs), notably methylation, acetylation, and phosphorylation. PTMs have long been associated with neurodegenerative diseases, including AD, FTD, and ALS. A less investigated PTM is citrullination, where arginine is irreversibly converted to citrulline by peptidyl arginine deiminases (PADs). Recently, we found TDP-43 citrullination is a marker of TDP-43 proteinopathy progression, with the citrullination site potentially affecting different aspects of TDP-43 pathology. We were interested in further investigating the role of neuronal PAD activity in TDP-43 pathology, to do so we over-expressed PAD4 in cortical and hippocampal neurons of aged non-transgenic and FTD mice. We found that PAD4 over-expression reduced hippocampal activity (synaptic strength and LTP), induced hippocampal hyper-excitability, increased hippocampal phosphorylation and aggregation of TDP-43 and altered the metabolic profile of both non-transgenic and FTD mice.

Disclosures: S. Lundt: None. **P. Rocha-Rangel:** None. **J. Hunt:** None. **D.C. Lee:** None. **M.B. Selenica:** None.

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PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.14/V13

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

Support: NIH Grant R15NS125394
NIH Grant F31NS141641

Title: C9orf72 Proteinopathy is Associated with Distinct Histone Post Translational Modification and Chromatin State Changes

Authors: *R. FISHER[1], P. RAMCHAND[2], S. N. COBOS[3], M. TORRENTE[2]; [1]City Univ. of New York, Brooklyn, NY; [2]Brooklyn College/ CUNY, Brooklyn, NY; [3]The Grad. Ctr., Long Island City, NY

Abstract: Frontotemporal Dementia (FTD) is a fatal and incurable Alzheimer’s Disease Related Dementia leading to degeneration of cortical neurons in the frontal and temporal lobes of the

brain. Due to shared genetics and occurrence, FTD exists on a disease continuum with Amyotrophic lateral sclerosis (ALS), a fatal motor neuron degenerative disease. Hexanucleotide repeat expansions (HREs) in chromosome 9 open reading frame 72 (C9orf72) are one of the most common causes of FTD/ALS. HREs lead to the formation of aggregate-prone toxic dipeptide repeat proteins that are connected to distinct epigenetic signatures. Alterations in various epigenetic mechanisms, such as histone post-translational modifications and changes to chromatin structure, have been implicated in FTD/ALS. Changes in phosphorylation on serine 10 of histone H3 (H3S10ph) occur in yeast over-expressing the toxic DPR, Poly-PR. H3S10ph ChIP-seq reveals genomic instability due to loss of heterochromatin, and telomeric maintenance. Fibroblasts derived from patients bearing C9orf72 expansions recapitulate H3S10ph changes and reveal differential enzymatic accessibility profiles as well as concurrent changes in a histone PTM linked to constitutive heterochromatin, H3K9me3. Furthermore, C9 iPSC derived cortical neurons reveal histone PTM changes in agreement with heterochromatin breakdown. These findings suggest that defects in heterochromatin stability are connected to C9orf72 expansions and proteinopathy. Altogether, this study illuminates novel epigenetic mechanisms and potential disease treatment targets.

Disclosures: R. Fisher: None. **S.N. Cobos:** None. **M. Torrente:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.15/V14

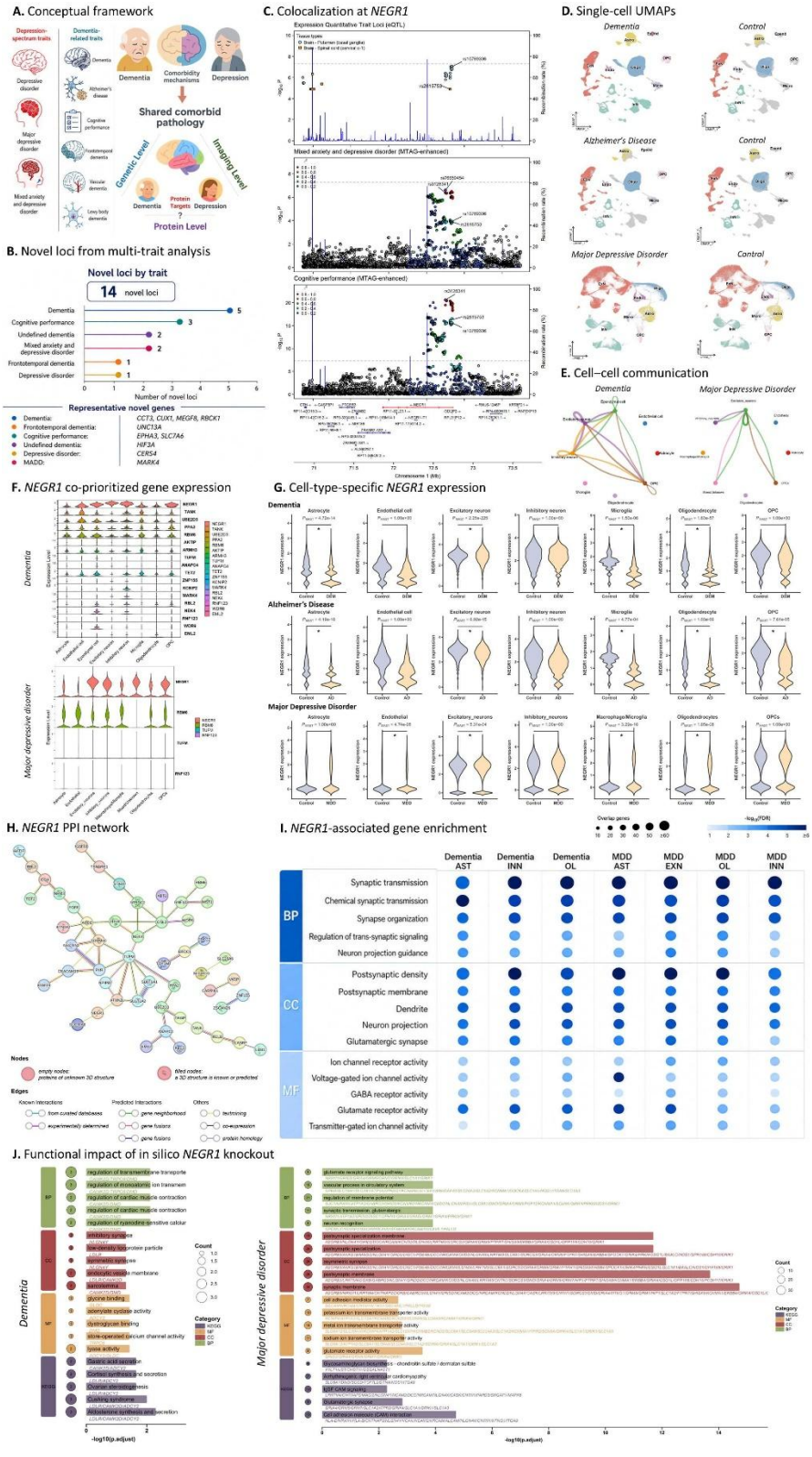
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Collaborative Research Fund (Project No. C5082-25E) from the Research Grants Council of the Hong Kong Special Administrative Region, P. R. China
General Research Fund (Project No. 15101422) from the Research Grants Council of the Hong Kong Special Administrative Region, P. R. China
Internal grant (P0051278) from The Hong Kong Polytechnic University

Title: A central role for neuronal growth regulator 1 (NEGR1) in the comorbidity of dementia and depression

Authors: *H. DING[1], N. LI[2], G. W. CHENG[1], J. LAN[1], H. CHEN[1], K. OH[3,1], Y. MAO[1], W. CHAN[1], M. YUE[1], N. NG[1,4], G. YIP[1,5], W. XIA[6], L.-T. LIN[1], G.-Y. LI[1], J. YOO[1];
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Abstract: Dementia and depression are highly comorbid, yet the molecular basis of their co-occurrence remains unclear. To resolve this, we integrated cross-trait GWAS (multi-trait analysis, MTAG), human-brain single-nucleus RNA-seq, protein-interaction analysis, and *in silico* gene knockout across depression-spectrum (depressive disorder, major depressive disorder [MDD], mixed anxiety-depressive disorder [MADD]) and dementia-related traits (dementia, Alzheimer's disease [AD], frontotemporal dementia, cognitive performance). MTAG identified 14 novel risk loci, including *CCT3*, *CUX1*, *MEGF8*, *UNC13A*, *EPHA3*, and *MARK4*. Bayesian colocalization at the 1p31.1 locus (lead variants rs10789336, rs2815753, and rs3128341) identified a shared causal variant linking *NEGR1* expression to MADD and cognitive performance. Across dementia, AD, and MDD brains, *NEGR1* showed cell-type-specific dysregulation, being markedly downregulated in astrocytes, microglia, and oligodendrocytes (P=1.6e-57) and altered in excitatory neurons (P=2.3e-225) in dementia, with concomitant remodeling of glia-neuron signaling. Within a protein-interaction network, NEGR1 and co-prioritized proteins (TUFM, UBE2D3, RBM6) clustered with AD-risk proteins APOE, TOMM40, and NECTIN2. Functionally, *NEGR1*-associated genes were enriched for synaptic transmission, postsynaptic specialization, and glutamate and GABA receptor activity, and *in silico NEGR1* knockout preferentially perturbed glutamatergic signaling and cell adhesion molecule (CAM) interactions in MDD. These results establish NEGR1, an IgLON-family cell adhesion molecule, as a shared, cell-type-specific determinant of dementia-depression comorbidity acting through synaptic adhesion and glutamatergic signaling and nominate it as a candidate cross-disorder therapeutic target.



Disclosures: H. Ding: None. **N. Li:** None. **G.W. Cheng:** None. **J. Lan:** None. **H. Chen:** None. **K. Oh:** None. **Y. Mao:** None. **W. Chan:** None. **M. Yue:** None. **N. ng:** None. **G. Yip:** None. **W. Xia:** None. **L. Lin:** None. **G. Li:** None. **J. Yoo:** None.

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PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.16/V15

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: Extracellular Vesicles from hiPSC-derived Neural Stem Cells Can Reverse Advanced Age-Related Cognitive Impairments with Alleviation of Neuroinflammaging and mTOR activation

Authors: *S. VENKATA GANESH, A. SAHITHI, G. SHANKAR, L. N. MADHU, V. RAO, M. KODALI, S. RAO, P. M. MANDHYAN, M. GUPTA, C. HUARD, M. DCUNHA, K. SRIVASTVA, B. SHUAI, A. K. SHETTY;
Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Texas A&M Univ., College Station, TX

Abstract: Brain aging is driven by chronic, sterile inflammation known as neuroinflammaging, which typically accompanies increased mechanistic target of rapamycin (mTOR) signaling and reduced autophagy, all of which can contribute to age-related cognitive and mood impairments. Our previous studies have shown that extracellular vesicles (EVs) from human-induced pluripotent stem cell (hiPSC)-derived neural stem cells (NSCs), referred to as hiPSC-NSC-EVs, carry a therapeutic cargo comprising miRNAs and proteins that modulate neuroinflammaging, mTOR signaling, and autophagy in models of aging and Alzheimer's disease. Here, we investigated whether hiPSC-NSC-EVs treatment could reverse pre-existing cognitive impairments in aged mice. Cognitively impaired 23.5-month-old C57BL6/J mice received two intranasal doses of either hiPSC-NSC-EVs (50 × 10^9/dose, Aged-EVs group) or vehicle (Aged-Veh group), spaced two weeks apart. Behavioral testing was performed between 24.5 and 25.5 months of age, followed by analysis of brain tissues. hiPSC-NSC-EV treatment produced significant cognitive recovery in aged mice, restoring the ability to perceive minor changes in their environment in an object location task, to track sequences of events over time in a temporal pattern processing task, and to improve spatial working memory in a delayed Y-maze task. Whereas mice in the Aged-Veh group remained impaired in all of these tasks. hiPSC-NSC-EVs treatment also prevented anhedonia, a symptom of age-related mood decline. In the medial prefrontal cortex and hippocampus, hiPSC-NSC-EVs treatment reduced astrocyte hypertrophy and decreased microglia harboring the NLR family pyrin domain-containing 3 (NLRP3)inflammasome complex. Biochemical analysis confirmed robust reductions in the concentrations of both mediators (NLRP3 and cleaved caspase-1) and end products (interleukin-1 beta [IL-1β] and IL-18) ofNLRP3 inflammasome activation, alongside reducing the concentration of cyclic GMP-AMP synthase and stimulator of interferon genes (cGAS-STING)

signaling pathway proteins such as cGAS, phosphorylated STING (pSTING), and interferon-alpha in hiPSC-NSC-EVs-treated mice. hiPSC-NSC-EVs treatment also reduced mTOR signaling, as evidenced by a lower p-mTOR/pan-mTOR ratio and enhanced autophagy, as shown by increased microtubule-associated protein 1 light chain 3 beta (MAP1LC3B) and reduced p62(sequestosome 1) in the hippocampus. These results demonstrate that intranasal hiPSC-NSC-EVs treatment can reverse advanced age-related cognitive decline by reducing neuroinflammaging and mTOR activation while restoring neuronal autophagy.

Disclosures: S. Venkata Ganesh: None. **A. Sahithi:** None. **G. Shankar:** None. **L.N. Madhu:** None. **V. Rao:** None. **M. Kodali:** None. **S. Rao:** None. **P.M. Mandhyan:** None. **M. Gupta:** None. **C. Huard:** None. **M. Dcunha:** None. **K. Srivastva:** None. **B. Shuai:** None. **A.K. Shetty:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.17/V16

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

Support: This work is supported by a grant from the Department of Defense (W81XWH-22-1-0565 to A.K.S.)

Title: Extracellular Vesicles Released by Microglia Derived from iPSCs of Gulf War Illness Veterans Can Drive Neuroinflammation and Trigger Cognitive Dysfunction

Authors: *S. RAO[1], L. N. MADHU[1], R. S. BABU[1], S. VENKATA GANESH[1], M. GUPTA[1], K. CASE[2], A. LEMAIRE[1], M. KODALI[1], S. REDDY[1], P. TARALE[1], B. SHUAI[1], X. RAO[1], C. FAN[1], M. DCUNHA[1], P. W. BAAS[2], K. SULLIVAN[3], A. K. SHETTY[1];
[1]Inst. for Regenerative Medicine, Dept. of Cell Biol. and Genetics, Texas A&M Univ. N, College Station, TX; [2]Dept. of Neurobio. and Anatomy, Drexel Univ. Col. of Med., Philadelphia, PA; [3]Dept. of Envrn. Health, Boston Univ. Sch. of Publ. Hlth., Boston, MA

Abstract: Gulf War Illness (GWI) is a multi-symptom illness affecting over a third of the 700,000 veterans who served in the first Gulf War. Microglia, the primary immune cells in the brain, are thought to be the major mediators of chronic neuroinflammation and cognitive dysfunction in GWI. However, the mechanisms underlying the maintenance or exacerbation of chronic neuroinflammation in the GWI brain remain unknown. This study compared the characteristics of extracellular vesicles (EVs) released by microglia derived from induced pluripotent stem cells (iPSCs) generated from Veterans with GWI or control Veterans. We generated microglia from iPSC lines derived from 3 Veterans with GWI (GWI-V iPSCs) and 3 Veterans without GWI (C-V iPSCs). Differentiated microglia from these iPSC lines expressed specific microglial markers, including TMEM119, CD11B, CX3CR1, and IBA-1. While

microglia from both GWI-V and C-V groups demonstrated phagocytic activity, the phagocytic ability of microglia was lower in the GWI-V group. Furthermore, microglia from both GWI-V and C-V groups responded to LPS and IFN-γ exposure by increasing TNFα and IL-6 release, but the response of microglia from the GWI-V group was higher. Notably, EVs isolated from the conditioned media of GWI-V microglial cultures increased complement C3 release in astrocyte cultures, whereas EVs from C-V microglial cultures did not, implying that GWI-V-EVs can propagate neuroinflammation. Small RNA sequencing and proteomic analysis of GWI-V-EVs and C-V-EVs revealed differentially expressed miRNAs and proteins in GWI-V-EVs, which can promote neuroinflammation, neurodegeneration, metabolic dysfunction, and immune imbalance. Next, GWI-V-EVs or C-V-EVs were administered intranasally to 6-month-old naive C57BL6 mice to determine whether GWI-V-EVs can promote neuroinflammation in a healthy brain. Three weeks after EV administration, mice receiving GWI-V-EVs showed impairments in object location memory and pattern separation tasks; in contrast, mice receiving C-V-EVs showed no such impairment. At 2.5 months post-EV administration, hippocampal analysis revealed that mice receiving GWI-V-EVs displayed increased microglial reactivity, elevated concentrations of multiple proteins involved in NLRP3 inflammasome activation, and lower numbers of newly born doublecortin-positive neurons, compared with naive mice and mice receiving C-V-EVs. Collectively, the results demonstrate that EVs released by microglia derived from iPSCs of GWI veterans can drive neuroinflammation and trigger hippocampus-dependent cognitive and memory dysfunction, associated with decreased hippocampal neurogenesis.

Disclosures: S. Rao: None. **L.N. Madhu:** None. **R.S. Babu:** None. **S. Venkata Ganesh:** None. **M. Gupta:** None. **K. Case:** None. **A. LeMaire:** None. **M. Kodali:** None. **S. Reddy:** None. **P. Tarale:** None. **B. Shuai:** None. **X. Rao:** None. **C. Fan:** None. **M. Dcunha:** None. **P.W. Baas:** None. **K. Sullivan:** None. **A.K. Shetty:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.18/V17

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

Support: This work is supported by a grant from the Department of Defense (W81XWH-22-1-0565 to A.K.S.)

Title: Effects of Curcumin on the Pathological Profile of Extracellular Vesicles released by Microglia from iPSCs of a Veteran with Gulf War Illness

Authors: *M. DCUNHA[1], S. RAO[1], S. VENKATA GANESH[1], L. N. MADHU[1], K. CASE[2], B. SHUAI[1], C. FAN[1], P. W. BAAS[2], K. SULLIVAN[3], A. K. SHETTY[1];
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Philadelphia, PA; [3]Envrn. Hlth. Dept, Dept. of Envrn. Health, Boston Univ. Sch. of Publ. Hlth., Boston, MA

Abstract: Chronic neuroinflammation is a key driver of persistent cognitive dysfunction in Gulf War Illness (GWI), with activated microglia playing a central role. Extracellular vesicles (EVs) released by these microglia may carry proinflammatory molecules that could worsen brain inflammation and impair neuronal and glial function. This study examined whether curcumin, a natural anti-inflammatory compound, can reduce proinflammatory responses in microglia derived from induced pluripotent stem cells (iPSCs) of a GWI veteran. We differentiated microglia from hiPSCs of a Veteran with GWI and treated them with different doses of curcumin (12.5, 25, or 50 μM) for 24 hours. Culture supernatants were analyzed for pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α. Curcumin significantly reduced IL-1β release from microglia at all tested concentrations. The concentrations of IL-6 and TNF-α were decreased with 25 μM or 50 μM of curcumin treatment. Since 25 μM curcumin reduced the release of all three inflammatory cytokines, it was selected as the optimal dose for studying EVs released by curcumin-treated GWI-veteran-derived microglia. EVs isolated from untreated and curcumin-treated GWI microglia were administered to hiPSC-derived mature astrocyte cultures. Astrocyte activation was assessed by measuring the release of complement component 3 (C3). EVs derived from untreated GWI microglia induced increased C3 release from astrocytes, indicating the proinflammatory activity of such EVs. In contrast, EVs from curcumin-treated microglia significantly attenuated this response. To probe curcumin-mediated effects further, EVs (30 billion) from untreated or curcumin treated GWI microglia were administered intranasally to naïve C57BL/6 mice. Two weeks later, the animals were tested with an object-location memory task and a spontaneous alternation task in a Y-maze. Mice receiving GWI microglia-derived EVs exhibited cognitive impairment as they were unable to perceive minor changes in their environment in the object location task, whereas mice receiving EVs from curcumin-treated GWI microglia showed no such impairments. Similarly, mice receiving GWI microglia-derived EVs showed a lower percentage of right choices in the spontaneous alternation task than naïve mice. However, such behavior was not observed in mice receiving EVs from curcumin-treated GWI microglia. These findings demonstrate the potential of curcumin to suppress proinflammatory activity in GWI-veteran-derived microglia and to alter the proinflammatory molecular cargo in EVs released by them. Curcumin treatment may thus help restrain neuroinflammation in veterans with GWI.

Disclosures: M. Dcunha: None. **S. Rao:** None. **S. Venkata Ganesh:** None. **L.N. Madhu:** None. **K. Case:** None. **B. Shuai:** None. **C. Fan:** None. **P.W. Baas:** None. **K. Sullivan:** None. **A.K. Shetty:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.19/V18

Topic: B.09. Glial Mechanisms

Support: NIH Grant NS104994

Title: Effects of CLEC7A deficiency in cerebellar postnatal development and in NPC1 deficiency associated pathology

Authors: G. BELT, N. GONZALEZ CUN, ***I. SOTO REYES**;
Providence Col., Providence, RI

Abstract: Proliferative region-associated microglia (PAM) are a transient microglial population found in developing white matter regions that highly express genes such as Clec7a, Spp1, and Apoe. While these genes are absent from homeostatic adult microglia, they are re-expressed in activated microglia associated with neurodegenerative diseases, including Niemann-Pick disease type C (NPC1). In this study, we investigated the role of CLEC7A in microglial activation and neurodegeneration in $Npc1^{nmf164}$ mice, as well as its contribution to postnatal microglial development in the cerebellum. At 60 days of age, CLEC7A deficiency attenuated microglial activation in $Npc1^{nmf164}$ mice, as evidenced by reduced microglial volume and amelioration of morphological changes associated with neurodegeneration. Although microglial volume remained elevated relative to wild-type (WT) mice, $Npc1^{nmf164}$/$Clec7a^{-/-}$ mice exhibited significantly smaller microglia than Npc1nmf164 mice, suggesting that CLEC7A contributes to the activated microglial phenotype. Furthermore, at 90 days of age, myelin basic protein (MBP) levels were significantly reduced in Npc1nmf164 mice but preserved in $Npc1^{nmf164}$/$Clec7a^{-/-}$ mice, indicating that loss of CLEC7A may protect against myelin deficits associated with NPC1 neurodegeneration. Interestingly, CLEC7A deficiency also altered normal postnatal cerebellar development. Although microglial morphology was largely unchanged during early postnatal stages, $Clec7a^{-/-}$ mice exhibited increased IBA1 immunoreactivity, reduced MBP immunoreactivity and protein levels, and deficits in ladder rung walking performance. These findings suggest that CLEC7A contributes to microglial maturation, myelination of Purkinje cell axons, and motor function. Ongoing studies are examining microglia-axon interactions to determine whether CLEC7A regulates axonal refinement during development. Together, these findings identify a dual role for CLEC7A in the cerebellum. While CLEC7A promotes microglial activation and myelin pathology during NPC1 neurodegeneration, it also appears necessary for normal microglial development and myelination in the healthy cerebellum.

Disclosures: G. Belt: None. **N. Gonzalez Cun:** None. **I. Soto Reyes:** None.

Poster

PSTR220: Neurodegeneration Beyond Alzheimer's Disease: Other Dementias and Proteinopathies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR220.20/V19

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

Support: NIH/NIA Grant AG072510

Title: Impaired pS14-Rpn6-dependent Proteosome activation accelerates Alzheimer's Disease pathology in 5XFAD mice

Authors: *R. BERAGAMA ARACHCHI[1], X. WANG[2], H. WANG[1];
[1]Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Div. of Biomed. and Translational Sci., Univ. of South Dakota Sanford Sch. of Med., Vermillion, SD

Abstract: Proteasome dysfunction and impaired protein homeostasis are increasingly recognized as contributors to aging and Alzheimer's disease (AD). Phosphorylation of the 19S proteasome regulatory subunit Rpn6 at Ser14 (pS14-Rpn6) enhances 26S proteasome activity and promotes the degradation of ubiquitinated proteins. Although pS14-Rpn6 mediated proteasome activation has been implicated in protection against proteotoxic stress, its role in AD progression remains unclear. We investigated the impact of impaired pS14-Rpn6 signaling on AD-associated neuropathology using wild-type (WT), $Rpn6^{S14A/S14A}$ knock-in (S14AA), 5xFAD, and S14AA:5xFAD mice at 12 months of age. The S14AA mutation prevents phosphorylation of Rpn6 at Ser14 and disrupts proteasome activation. Biochemical analyses demonstrated reduced proteasome activity in the brain cortex of S14AA and S14AA:5xFAD mice compared with their WT-Rpn6 controls. Impaired proteasome activation was associated with significantly increased amyloid pathology in S14AA:5xFAD mice, including enhanced Thioflavin-S-positive plaque burden and elevated amyloid-β levels relative to 5xFAD littermates. Increased amyloid accumulation was accompanied by elevated oxidative damage, increased activation of DNA damage response pathways, enhanced cellular senescence and apoptotic signaling, increased astrocytic and microglial reactivity, and reduced PSD95-synaptophysin apposition, indicative of synaptic dysfunction. These findings identify pS14-Rpn6 mediated proteasome activation as an important regulator of AD-associated neuropathology and demonstrate that disruption of this pathway accelerates amyloid accumulation and downstream neurodegenerative processes. Collectively, our results support a protective role of pS14-Rpn6 mediated proteasome activation in maintaining neuronal proteostasis and limiting disease progression in AD.

Disclosures: R. Beragama Arachchi: None. **X. Wang:** None. **H. Wang:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.01/V20

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

Title: Development and Characterization of Highly Specific Rabbit Monoclonal Antibodies for Sensitive pTau Detection in Alzheimer's Disease Tissue and Biofluids

Authors: *A. AIELLO[1], L. LIU[2], D. MULHERN[1], S. MULLENBROCK[1], M. STUMP[1], E. ESTABROOK[1], K. MACCHI[1], S. SINGH[1], T. C. WIEDERHOLD[1], R. W. CHO[1];

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Abstract: The detection of fluid-based biomarkers for Alzheimer's Disease (AD) increasingly relies on high-sensitivity immuno-technologies to detect disease-relevant analytes in complex matrices. Among these, Tau phosphorylated at threonine 217 (pTau217) has emerged as a strong correlate of various tauopathies, including AD. We aimed to develop and characterize highly specific and sensitive rabbit monoclonal antibodies (mAbs) against various Tau regions, isoforms, and PTMs, including a highly specific mAb clone (E9Y4S) against pTau217, to enhance detection of Tau isoforms and PTMs across multiple immuno-based platforms. Furthermore, we sought to investigate how pTau217, detected in combination with antibodies targeting other regions of Tau, might improve discrimination between AD and non-AD samples. Recombinantly generated monoclonal antibodies targeting specific Tau isoforms and PTMs were validated for specificity using western blot (WB), immunoprecipitation (IP), peptide dot blot, and ELISA. Binding kinetics and affinity of these antibodies were measured and compared against leading commercially available antibodies. We further evaluated antibody pairs in a sandwich ELISA format using human and rodent tissues/biofluids and integrated specific mAb pairs into a high-sensitivity platform, enabling discrimination of AD from non-AD CSF samples. We also developed ELISA-compatible semi-synthetic standards (pTau217, pTau181, and pTau205) to enable quantitative measurement of Tau PTMs. In summary, we report the development of a mAb-based tool kit that is compatible with standard WB/IP and high-throughput, pair-based platforms that can enable and accelerate the development of Tau-based biofluid assays.

Disclosures: A. Aiello: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **L. Liu:** None. **D. Mulhern:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **S. Mullenbrock:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **M. Stump:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **E. Estabrook:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **K. Macchi:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **S. Singh:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **T.C. Wiederhold:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc. **R.W. Cho:** A. Employment/Salary (full or part-time):; Cell Signaling Technology, Inc..

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.02/V21

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

Support: NINDS Grant R01NS129407
NINDS Grant R01NS133569
NIA Grant P30AG086404

Title: Intestinal permeability in long COVID patients with neurocognitive symptoms is associated with Alzheimer's disease biomarkers

Authors: *L. O'CONNELL[1], D. COE[1], S. M. HOBSON[2], N. SHAFF[1], H. LIN[5,6], A. BIRG[6,5], S. G. RYMAN[1,3], E. ERHARDT[4], A. CAPRIHAN[1], A. A. VAKHTIN[1];
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Abstract: Title: Intestinal permeability in long COVID patients with neurocognitive symptoms is associated with Alzheimer's disease biomarkers
Authors: Lizza O'Connell, Devin Coe, Sasha Hobson, Dhruba Adhikari, Nicholas Shaff, Henry Lin, Aleksandr Birg, Sephira Ryman, Erik Erhardt, Arvind Caprihan, Andrei Vakhtin
Neurocognitive post-acute sequelae of COVID-19 (PASC) can follow SARS-CoV-2 infection chronically. Emerging evidence points to a link between PASC and increased risk for Alzheimer's disease and related dementias (ADRD). In light of increasing recognition of gut-brain interactions in both PASC and ADRD, the present study examined the relationships between gut permeability and amyloid beta 42/40 ratios in PASC patients with neurocognitive symptoms (PASC+) as well as in PASC- controls who recovered fully after their SARS-CoV-2 infections. All participants had mild, non-hospitalized SARS-CoV-2 infections at least 3 months prior to study participation. PASC- control participants (n=44) had no lasting PASC symptoms, and PASC+ participants (n=39) reported chronic neurocognitive symptoms such as brain fog and fatigue. All participants followed identical dietary restrictions prior to the study in order to normalize their intestinal microbiomes. Quanterix Simoa platform assays were used to quantify plasma $A\beta_{42}$ and $A\beta_{40}$. Thermo Fisher kits were used to quantify zonulin and fatty acid-binding protein 2 (FABP2) - markers of paracellular and transcellular intestinal permeability, respectively. Zonulin levels were significantly higher in the PASC+ group relative to PASC- controls ($p = 0.004$). Higher levels of zonulin, but not FABP2, were significantly predictive of lower $A\beta_{42}/40$ ratios in the PASC+ group ($p = 0.030$). However, no such relationship was observed in the PASC- control participants ($p = 0.442$). The results bolster the growing evidence for the involvement of the gut in PASC, and implicate elevated paracellular gut permeability as a possible link between PASC and ADRD risk.

Disclosures: L. O'Connell: None. **D. Coe:** None. **S.M. Hobson:** None. **N. Shaff:** None. **H. Lin:** None. **A. Birg:** None. **S.G. Ryman:** None. **E. Erhardt:** None. **A. Caprihan:** None. **A.A. Vakhtin:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.03/V22

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

Support: NINDS Grant R01NS129407
NINDS Grant RO1NS133569
NIGMS Grant P30AG086404

Title: Chronic Astrogliosis and Cerebrovascular Dysfunction in Post-Acute Sequelae of COVID-19

Authors: *D. COE[1], L. H. O'CONNELL[1], S. M. HOBSON[3], N. SHAFF[1], H. LIN[4], A. BIRG[4], S. G. RYMAN[2,5], E. ERHARDT[4], A. CAPRIHAN[1], A. A. VAKHTIN[1];
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Abstract: Title: Chronic Astrogliosis and Cerebrovascular Dysfunction in Post-Acute Sequelae ofCOVID-19**Authors:** Devin Coe, Lizza O'Connell, Sasha Hobson, Dhruba Adhikari, Nick Shaff,Henry Lin, Alex Birg, Sephira Ryman, Erik Erhardt, Arvind Caprihan, Andrei Vakhtin**Abstract:** Post-acute sequelae of COVID-19 (PASC) include persistent symptoms thatare often neurocognitive. Our group recently characterized dysfunctionalcerebrovascular dynamics that follow mild SARS-CoV-2 infection. To elucidate thesefindings, here we evaluated post-infection trajectories of glial fibrillary acidic protein(GFAP) – a marker of astrocytic damage – in a group of long COVID patients (PASC+)as well as PASC- controls who recovered fully after their SARS-CoV-2 infections. Inaddition, we evaluated the relationships between GFAP levels and cerebrovascularreactivity (CVR) to hypercapnia – a functional metric of vascular health in the brain.Participants with prior mild SARS-CoV-2 infections were classified as PASC+ (N= 39) orPASC− (N=46) based on the presence or absence of ongoing neurocognitive symptomsfollowing COVID-19. Plasma GFAP concentrations were quantified using the QuanterixSimoa platform, and fMRI during an intermittent hypercapnia task was used to quantifyCVR magnitude (%BOLD/mmHg). Group analyses revealed significantly elevated GFAPlevels in PASC+ patients relative to PASC− controls ($p = 0.008$). Within the PASC+group, GFAP increased as a function of time-since-infection ($p = 0.005$), whereas nosuch relationship was observed in the PASC− participants ($p = 0.897$). Further, higherGFAP levels were associated with reduced CVR magnitude in PASC+ participants ($p =0.044$). In contrast, no significant relationship between GFAP and CVR magnitude wasobserved in PASC− controls ($p = 0.858$). The findings suggest that PASC may involvechronic, and potentially worsening, astrogliosis following mild SARS-CoV-2 infection –a pattern not observed in the PASC- controls who experienced no lasting post-infectionsymptoms. Further, the PASC-related astrocytic damage appears to drivecerebrovascular dysfunction, which may represent a mechanism underlying thepersistent neurocognitive symptoms often seen in PASC.**Funding:** R01NS129407, R01NS133569, P30AG086404

Disclosures: D. Coe: None. **L.H. O'Connell:** None. **S.M. Hobson:** None. **N. Shaff:** None. **H. Lin:** None. **A. Birg:** None. **S.G. Ryman:** None. **E. Erhardt:** None. **A. Caprihan:** None. **A.A. Vakhtin:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.04/V23

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

Title: Methylation-based deconvolution of plasma cfDNA for cell-type-resolved detection of neurodegeneration in Alzheimer's disease and other conditions

Authors: *C. A. POLLARD;
Renew Biotechnologies, Pleasant Grove, UT

Abstract: Blood-based biomarkers are improving early detection and staging in neurodegenerative disease, but current assays primarily reflect aggregate pathology or generalized neuronal injury and provide limited insight into which neuronal populations are affected. Circulating cell-free DNA (cfDNA) offers a complementary biomarker substrate because it retains DNA methylation patterns linked to tissue and cellular origin. However, neuron-derived cfDNA is expected to represent only a small fraction of total circulating cfDNA, creating technical challenges for low-input cell-of-origin analysis.

Here, we evaluated whether native nanopore methylation sequencing could support both brain methylation atlas generation and downstream cfDNA cell-of-origin classifier development in neurodegenerative disease. Using whole-genome native nanopore sequencing, methylation reference profiles were generated from primary human cortical, dopaminergic, and spinal motor neurons, as well as astrocytes, microglia, and Schwann cells. Cell-type-informed classifiers were developed from differentially methylated regions relative to pooled plasma background and first evaluated in silico using dilution series designed to model physiologic admixture.

Classifiers were then applied to a filtered cohort of 137 blood plasma samples from individuals with mild cognitive impairment (MCI, n = 5), Alzheimer's disease (AD, n = 35), Parkinson's disease (PD, n = 37), amyotrophic lateral sclerosis (ALS, n = 39), and healthy controls (n = 21). Disease-associated elevations were observed in neuron-aligned cfDNA methylation signals corresponding to selectively vulnerable populations, including cortical signatures in AD and progressive MCI, dopaminergic signatures in PD, and spinal motor neuron signatures in ALS. These signals supported strong binary disease-versus-control discrimination (AUCs > 0.97) and remained informative in more clinically relevant multi-disease comparisons, where combined neuronal classifiers achieved AUCs > 0.85. Repeated cross-validation, comparisons between covariate-only and methylation-only models, and PCA-based assessment of global technical and demographic structure supported the conclusion that performance was not explained by a dominant batch or demographic effect alone.

Although the current atlas is not comprehensive and larger independent cohorts will be required, these findings support the feasibility of native cfDNA methylation sequencing as a cell-type-informed liquid biopsy framework for studying neurodegeneration from peripheral blood.

Disclosures: C.A. Pollard: A. Employment/Salary (full or part-time):; Full Time Employee at Renew Biotechnologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership Interest in Renew Biotechnologies.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.05/V24

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

Title: LoBio P1 - A microvolume liquid plasma collection system to enable decentralized testing of neurodegenerative disease biomarkers

Authors: *L. JIANG, S. VEMULAPATI;
Lo Biosciences, Inc., Rockville, MD

Abstract: Blood-based biomarkers have demonstrated utility in advancing Alzheimer's disease (AD) and other Dementias research, but venous blood collection limits the scope of clinical studies. For example, phlebotomists and laboratory equipment are needed to collect and centrifuge the blood to produce laboratory quality plasma, limiting patient recruitment to those near labs and potentially biasing study populations. To address these barriers, we developed the P1, a micro volume blood collection tube that separates liquid plasma from blood via magnetic bead immunocapture within minutes, offering an easy-to-use alternative to conventional centrifugation without compromising sample integrity.
The LoBio P1 is designed to be used by lay users to produce analytical-grade plasma from whole blood. After blood is collected in the squeezable P1 tube, magnetic beads passively capture blood cells via antibody binding. The tube is then placed on top of a magnet, and the bound cells are pulled to the bottom in minutes. The supernatant plasma is then squeezed into a standard blood collection tube for storage and analysis.
This study evaluated the P1 for measuring glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and phosphorylated tau 217 (p-Tau217) using the Simoa platform. Spiked samples were prepared by supplementing 22 healthy donor EDTA whole blood samples with cerebrospinal fluid from amyloid-positive AD patients to generate clinically meaningful biomarker concentrations. Pearson correlation was used to assess agreement between matched samples (centrifugation vs P1).
We observed strong correlation for all three analytes between P1 and centrifuged plasma: GFAP ($r = 0.97$), NfL ($r = 0.96$), and p-Tau217 ($r = 0.92$). These findings support the P1's potential as a viable sample collection method for decentralized AD biomarker testing. By enabling easier access to the collection of laboratory quality plasma samples, the LoBio P1 can substantially accelerate biomarkers research and clinical studies related to AD and other Dementias.

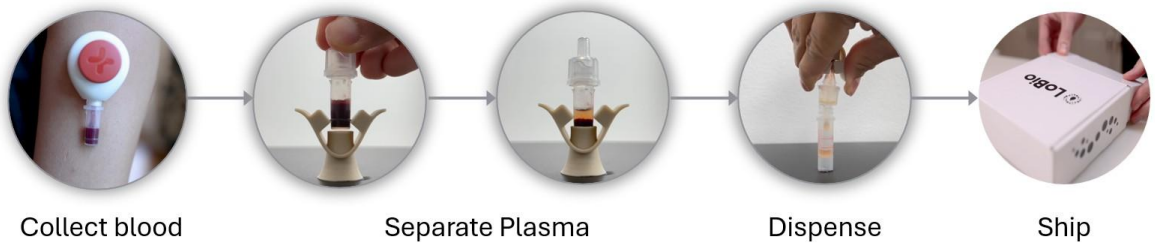


Figure 1. The P1 is a centrifuge-free, magnet-driven system for rapid and efficient plasma separation. The steps are: (1) Collect blood (shown here used with a Tasso+ upper arm lancet) and mix with beads inside the tube. (2) Place tube on a magnetic stand. (3) Cells and plasma separate automatically. (4) Squeeze the tube to dispense plasma.

Disclosures: L. Jiang: A. Employment/Salary (full or part-time):; Lo Biosciences, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lo Biosciences, Inc. **S. Vemulapati:** A. Employment/Salary (full or part-time):; Lo Biosciences, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute on Aging (NIA). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lo Biosciences, Inc..

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.06/V25

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

Support: Arizona Alzheimer's Consortium Blood Based Biomarker Pilot Grant

Title: Liver Dysfunction Inflates Circulating pTau217, Highlighting Brain Derived pTau217 as a More Reliable Biomarker

Authors: *E. GREIG[1], W. H. ROBB[2], M. DENKINGER[5], S. M. BOUCHAL[3,4], A. SINGH[5], T. J. HOHMAN[6], M. I. KORAN[1,2];
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Abstract: Blood-based measures of tau isoforms are increasingly used clinically to monitor and predict Alzheimer's disease (AD) pathology. Emerging evidence indicates that concentrations of peripheral biomarkers, including tau, are influenced by systemic organ dysfunction, limiting widespread clinical utility and confounding diagnosis. Current FDA-approved assays measure total tau (peripheral and central) and do not distinguish between protein abnormalities secondary to organ dysfunction and levels reflecting true brain pathology. In this longitudinal study, we evaluate total and brain-derived (BD) MAPT, pTau181, pTau217, and pTau231 in patients ~4 weeks before and 4-12 months after liver transplant (LT) to assess the stability of these blood-based biomarkers across the extremes of liver function. Serum concentrations of total and BD MAPT, pTau181, pTau217, and pTau231 were assessed via the NULISAseq 120-plex CNS Panel in 55 LT patients. Linear mixed-effects models assessed changes in tau levels pre- to post-LT and associations with changes in liver function assessed via Model for End-Stage Liver Disease (MELD) Score. Following LT, all total tau measures decreased after LT, as did BD-pTau181 and pTau231 at 4-months (β=-0.374, p=0.008; β=-0.887, p<0.001 respectively). Results were similar at 12-months. Notably, both BD-MAPT and BD-pTau217 did not significantly change after LT at either timepoint (p>0.05). Similarly, improvement in liver function was associated with decreases in all total tau levels, BD-pTau181, and BD-pTau231 but not with changes in BD-MAPT and BD-pTau217. All total tau biomarkers changed following LT, including the clinically implemented pTau217, suggesting these biomarkers be interpreted with caution in patients with liver dysfunction. Of note, BD-MAPT and BD-pTau217 did not change post-LT, suggesting that these biomarkers may be more reliable. Tau production and release from hepatocytes due to stress, or altered hepatic clearance of systemic tau, may be contributing to elevated levels of total tau compared to BD-tau. Total tau biomarkers should not be used in AD evaluation in pre-LT cases.

Disclosures: E. Greig: None. **W.H. Robb:** None. **M. Denkinger:** None. **S.M. Bouchal:** None. **A. Singh:** None. **T.J. Hohman:** None. **M.I. Koran:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.07/V26

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

Support: NIH Grant 1R43AG094412-01
Joseph Drown Fndn. Grant
T-Neuro research support
NIH Grant 1R21AG033394-01
NIH Grant 1R21NS054162-01

Title: T cell-based recognition of non-Abeta Amyloid Precursor Protein (APP) peptide epitope and protein in blood as potential pre-amyloid biomarkers for Alzheimer's and related Mild Cognitive Impairment (MCI)

Authors: *C. J. WHEELER[1], R. A. RISSMAN[2], A. P. SAGARE[4], J. BARLOW[3], J. WATANABE[5], D. VAN DAM[6], Y. VERMEIREN[7], P. DE DEYN[6];
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Abstract: Background: e Biomarkers for Alzheimer's disease (AD) are primarily based on amyloid beta, phosphorylated tau species and markers of neurodegenerative, which do not fully capture early disease induction or trajectory. We recently developed a CD8 T cell-induced mouse model that allowed development of a potentially pre-amyloid biomarker for AD that is based on quantification of age-related Amyloid Precursor Protein [APP] peptide-binding CD8 T ("hiT") cells in blood (PMID: 38995966) using an $APP_{471-479}$/Human Leukocyte Antigen(HLA)-A2 multimer (pHLA) and flow cytometry. Levels of hiT cells distinguished AD and related MCI from normal aging controls with high accuracy, but only HLA-A2-positive patients are testable with the APP-specific reagent, limiting its utility to ~50% of patients expressing HLA-A2.
Methods: Binding to a non-self ($_{ALIAPVHAV}$/HLA-A2) multimer was also observed by hiT cells in blood of HLA-A2-positive and HLA-A2-negative patients. We assessed binding and disease correspondence to this non-self pHLA by CD8 T cells from blood of HLA-A2-positive (n = 79) and -negative (n = 44) AD and MCI subjects, examined reproducibility of pHLA signal within normal blood specimens, and used a whole-blood antigen-induced reactivity (AIM) assay to examine T cell reactivity to APP protein in normal patients to expand assay format options independent of HLA-A2 restriction.
Results: In receiver-operating characteristic (ROC) analysis, the non-self pHLA binding in the HLA-A2-negative cohort revealed area under the curve (AUC) of 0.878 for AD and 0.816 for AD-related MCI ($P < 0.00001$, $\geq$78% sensitivity, $\geq$99% specificity), with disease tracking improved in the HLA-A2-positive cohort (AUC 0.912 for AD; 0.921 for AD-related MCI). We demonstrated signal reproducibility among cognitively normal cohorts from 4 distinct repositories and sample types (fresh and frozen whole blood, fresh PBMC, frozen buffy coats), provided CD8+ cells were present at physiological levels (minimally $\geq$2.5% and typically 5-40% of gated lymphocytes). Finally, we found significant CD4 and CD8 T cell reactivity to APP protein by AIM assay in normal patients.
Conclusion: Decreased pHLA multimer binding by CD8 T cells strongly corresponds to AD and MCI-AD in individuals, with one reagent being useful independent of HLA-A2 status, with signal levels reproducible in blood from distinct sources and handling conditions. Broader subpopulations of APP-reactive T cells were also detectable by AIM assay in normal patients. Together, this provides a working basis for expanding the utility of a potentially pre-amyloid blood biomarker for AD to all patients.

Disclosures: C.J. Wheeler: A. Employment/Salary (full or part-time):; T-Neuro Inc., University of California, Santa Cruz. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH

1R43AG094412-01. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); T-Neuro Inc., Ortega NeuroRx, NovAccess Global & StemVax LLC. **R.A. Rissman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH 1R43AG094412-01. F. Consulting Fees (e.g., advisory boards); T-NeuroDx. **A.P. Sagare:** None. **J. Barlow:** None. **J. Watanabe:** None. **D. Van Dam:** None. **Y. Vermeiren:** None. **P. De Deyn:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.08/V27

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

Support: NIH Grant AG079303

Title: CNS-Derived Extracellular Vesicles as Next-Generation Biomarkers of APOE4-Driven Neurodegeneration Following TBI

Authors: *M. CULLUM-DOYLE[1,2], M. S. PANIZZON[1], V. B. RISBROUGH[1], R. RISSMAN[2];
[1]Univ. of California San Diego, La Jolla, CA; [2]Alzheimer's Therapeut. Res. Institute, Univ. of Southern California, San Diego, CA

Abstract: Background: Traumatic brain injury (TBI) affects millions of people annually, yet doctors do not follow up on the chronic effects of the injury after acute care ends. Carriers of the apolipoprotein E4 (APOE4) allele face the highest risk for late-onset Alzheimer's disease (AD) and are particularly vulnerable to neurodegeneration following TBI. Analyzing free-floating plasma proteins as biomarkers fails to capture CNS-specific signals. We examined whether proteins in CNS-derived extracellular vesicle (EV) cargo would provide more sensitive biomarkers of neurodegeneration following TBI.
Methods: Using biobanked plasma from 1,062 male participants (mean age 68 years) in the Vietnam Era Twin Study of Aging, neuron-derived EVs (NEVs) and astrocyte-derived EVs (AEVs) were isolated via L1CAM and GLAST immunocapture, respectively. EVs were characterized by flow cytometry, nanoparticle tracking analysis, nanoimaging, and Western blot. Targeted proteomics for neurofilament light (NfL), Aβ42, Aβ40, total tau, and p-tau181 were conducted in plasma, NEV, and AEV cargo using Quanterix SIMOA, normalized to Flotillin-1 ELISA. TBI × APOE4 interactions were analyzed using mixed-effects models with False Discovery Rate corrections. Investigators were blinded to genotype and TBI history, and the male-only cohort design is acknowledged as a limitation.
Results: Analysis of NEV protein cargo revealed significant TBI × APOE4 interactions for NfL ($F=8.1$, $p=0.025$), Aβ42 ($F=4.87$, $p=0.048$), and total tau ($F=4.82$, $p=0.037$), scaling with injury

frequency and recency exclusively in APOE4 carriers. The absence of TBI history was associated with lower baseline NEV cargo in APOE4 carriers relative to non-carriers. These findings suggest the APOE4 allele impairs neuronal protein packaging under homeostatic conditions, a deficit that TBI significantly reverses. In AEV cargo, distinct cell-type-specific increases in these same signatures emerged, indicating differential protein sequestration between neurons and astrocytes in the context of TBI and APOE4 risk. No significant TBI × APOE4 interactions were detected in matched plasma for any biomarker (all $p>0.05$).
Conclusions: These results show that carrying the APOE4 allele impairs the sequestration of proteins into EVs by neurons and astrocytes following TBI. Significant increases in biomarkers of neurodegeneration suggest cumulative, sustained brain damage that can be measured years after injury. Undetectable in free-floating plasma, these EV biomarker signatures point to a chronic injury state after TBI and reveal a possible window for targeted interventions before neurodegeneration becomes irreversible.

Disclosures: M. Cullum-Doyle: None. **M.S. Panizzon:** None. **V.B. Risbrough:** None. **R. Rissman:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.09/V28

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

Support: NIH/NIA Grant No. R01AG078211
NIH/NIA Grant No. 1R01AG053961
NIH/NIA Grant No. R01NS130713
NIH/NIA Grant No. R01AG091689
NIH/NIA Grant No. R01AG0852729
NIH/NIA Grant No. R13AG069380
Dianne Isakson Distinguished Professorship
J. Seward Johnson Postdoctoral Fellowship in Aging Neuroscience

Title: Higher Plasma Markers of the Pesticide DDT Associate with Lower Plasma Amyloid-beta 42/40 Ratio and Reduced Cortical Thickness within the Temporal Lobe in Cognitively Healthy Older African Americans

Authors: *S. MOALLEMIAN[1], I. MHATRE-WINTERS[3], C. KIM[3], M. ISHAQ[1], D. ABDALLA[1], M. BUDAK[1], J. STINGONE[4], P. FACTOR-LITVAK[4], D. M. SCARISBRICK[2], J. R. RICHARDSON[3], M. A. GLUCK[1];
[1]Rutgers-The State Univ. of New Jersey, Newark, NJ; [2]Rutgers Robert Wood Johnson Med. Sch., Rutgers-The State Univ. of New Jersey, Scotch Plains, NJ; [3]Dept. of Physiol. and Pharmacol., Isakson Ctr. for Neurolog. Dis. Research, Univ. of Georgia, Athens, GA; [4]Colombia Univ., New York, NY

Abstract: Higher Plasma Markers of the Pesticide DDT Associates with Lower Plasma Amyloid-beta 42/40 Ratio and Reduced Cortical Thickness within the Temporal Lobe in Cognitively Healthy Older African Americans.Soodeh Moallemian, Isha Mhatre-Winters, Chunki Kim, Martina Ishaq, Demiana Abdalla, Miray Budak, Pam R. Factor-Litvak, Jeanette A. Stingone, David M. Scarisbrick, Jason R. Richardson, Mark A. Gluck**Background:** Alzheimer's disease (AD) is a multifactorial disease that begins decades before the clinical symptoms. Environmental toxicants may contribute to AD risk, but their relationship to established AD biomarkers remain poorly understood, particularly in African Americans, who are disproportionately affected by AD. Dichlorodiphenyldichloroethylene (DDE), a persistent metabolite of dichlorodiphenyltrichloroethane (DDT), has been associated with cognitive impairment and increased AD risk, but its links to plasma AD biomarkers and brain microstructure remain unclear.**Methods:** 44 cognitively healthy older African Americans (31 females; mean age = 71.6 ± 5.3 years) from the Pathways to Healthy Aging cohort underwent blood collection and structural MRI. Plasma DDE was quantified using gas chromatography–mass spectrometry and log-transformed. Plasma biomarkers included Aβ42/40 ratio, phosphorylated tau-231 (p-tau231). Plasma Aβ42/40 ratio and temporal lobe cortical thickness were analyzed using linear regression models adjusted for age, sex, and education.**Results**: Higher plasma DDE was associated with lower plasma Aβ42/40 ratio (standardized β = −0.42 per SD increase in log[DDE], 95% CI [−0.72, −0.11], p = 0.01; partial Spearman ρ = −0.35). This association remained significant among the participants with detectable DDE levels (β = −0.40, p = 0.024, n = 35) and after false discovery rate correction within the plasma biomarker domain (q = 0.04). Higher DDE was also associated with lower temporal cortical thickness, with the strongest effect observed in the right transverse temporal cortex (Heschl's gyrus, standardized β = −0.43, p = 0.006).**Conclusions:** Greater DDE exposure was associated with reduced plasma Aβ42/40 ratio and lower temporal lobe cortical thickness in cognitively healthy older African Americans, supporting a role for environmental toxicants in AD-related brain vulnerability.

Table . Statistical descriptives.

					Skewness		Kurtosis		Shapiro-Wilk	
	mean	S.D.	Min.	Max.	Skewness	SE	Kurtosis	SE	W	p
Age	71.54	5.32	62	85	0.40	0.36	-0.06	0.70	0.98	.573
Education	15.05	2.46	10	21	0.59	0.36	-0.09	0.70	0.94	.022
p -tau231	3.25	1.90	1.37	11.48	2.38	0.36	7.60	0.70	0.78	<.001
Log (p-tau231)	1.06	0.48	0.31	2.44	0.71	0.36	0.55	0.70	0.96	.179
Aβ42/40	0.05	0.01	0.03	0.06	-0.50	0.36	-0.00	0.70	0.97	.397
DDE	1.61	2.37	0.05	10.04	2.49	0.36	5.87	0.70	0.64	<.001
Log (DDE)	-0.50	1.58	-3.02	2.31	-0.32	0.36	-0.72	0.70	0.92	.004

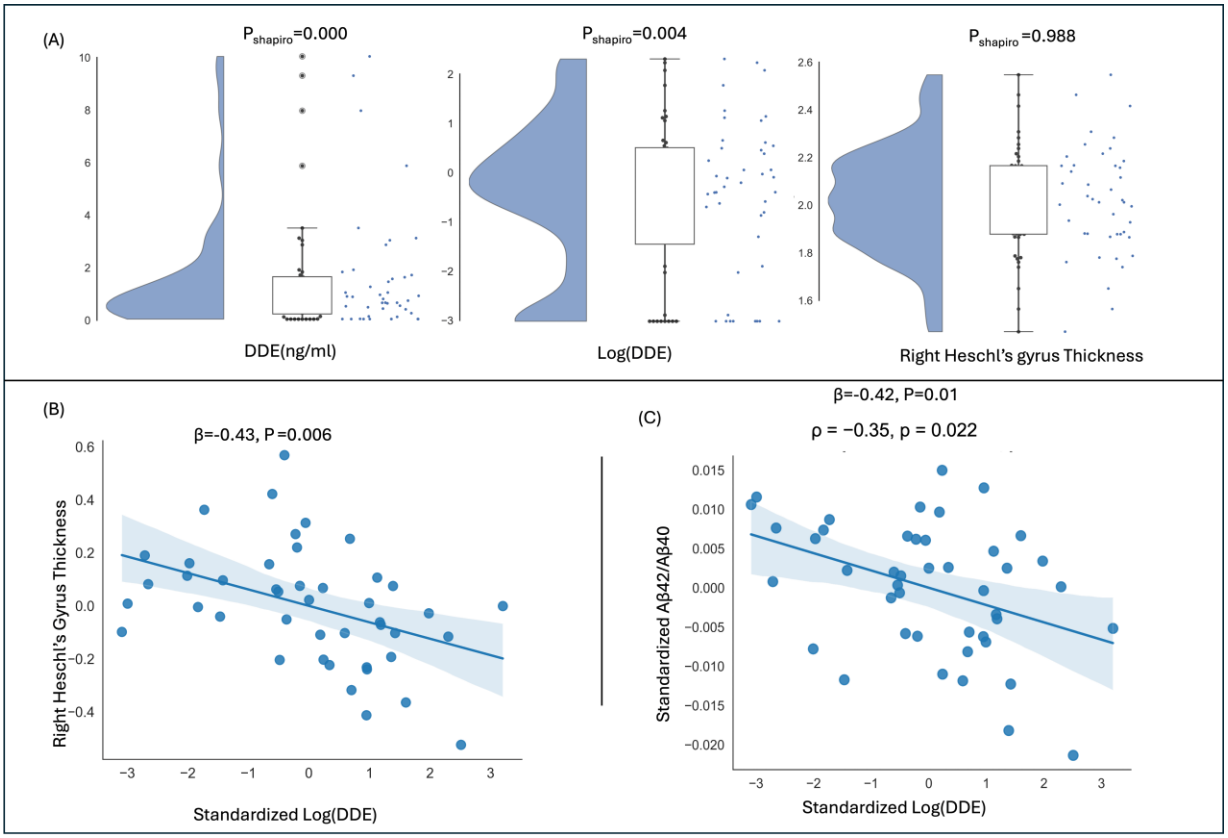


Figure 1. (A) Raincloud plots normalized to mean of 0, concentrations. (B) Scatterplot demonstrating the negative association between log (DDE) levels and (B) right Heschl's cortical thickness and (C) Aβ42/40 after controlling for age, sex, and education.

Disclosures: S. Moallemian: None. **I. Mhatre-Winters:** None. **C. Kim:** None. **M. Ishaq:** None. **D. Abdalla:** None. **M. Budak:** None. **J. Stingone:** None. **P. Factor-Litvak:** None. **D.M. Scarisbrick:** None. **J.R. Richardson:** None. **M.A. Gluck:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.11/W1

Topic:

Support: FairFaxWood foundation
FAU OURI program
FAU SMART Health

Title: Evidence for Canal-Like Lymphatic Networks that Mediate Confinement of High-Concentration Amyloid Beta for Brain Homeostasis

Authors: *R. TAO, G. SHIM, G. GIORDANO, G. CHAPAGAIN, H. PRENTICE;
Biomed. Sci., Florida Atlantic Univ., Boca Raton, FL

Abstract: The brain comprises four distinct fluid types that function as transport vehicles across five interconnected compartments: the CSF-filled ventricular system, the ISF-filled extracellular space, the blood-filled vascular system, the ISF-filled glymphatic space, and the lymphatic vasculature. All these fluid compartments have the potential to harbor Aβ. This study aimed to identify the primary compartment responsible for the containment, confinement, and subsequent clearance of Aβ from the brain. We hypothesized that this compartment must rapidly and actively sequester Aβ against concentration gradients, thereby preventing its free diffusion away from APP cleavage sites within the extracellular space, where it could otherwise induce neurotoxicity in parenchymal cells. Methodologically, Aβ distribution across these compartments was evaluated using PET co-registered with MRI. Leveraging data-science approaches, we screened approximately 10,000 raw imaging datasets from the Image Data Archive (https://ida.loni.usc.edu) and obtained a curated subset of florbetapir PET/MRI datasets. Given the scale of analysis, we focused on 12 patients with AD (N = 12) and 12 age- and sex-matched cognitively unimpaired controls (CU; N = 12). PET/MRI datasets were processed using three analytical pipelines: data-lossy, data-lossless, and data-enhanced approaches. In the data-lossy analysis, the majority of Aβ signal was removed, leaving only sparse focal hotspots within the brain parenchyma, consistent with traditionally described amyloid plaques. In contrast, the data-lossless analysis revealed a distinct topographic distribution of Aβ across the brain, scalp, and cervical regions in both AD and CU groups. The lowest concentrations (estimated <10 nM), largely undetectable by PET/MRI, were localized to CSF-filled compartments. Higher concentrations, ranging from 1 to 10 mM, were prominently observed in white matter regions and internal capsules—levels orders of magnitude above the established neurotoxic threshold in the ISF (~1 μM). In the data-enhanced analysis, Aβ signals appeared to be spatially confined within canal-like networks. These structures demonstrated direct connectivity to the peripheral lymphatic system and cervical lymph nodes and were consistently observed in both AD and control cohorts. Collectively, these findings suggest that Aβ is primarily sequestered within a cerebral lymph-filled vascular network. Despite the presence of high local concentrations (1-10 mM), Aβ appears to be proactively contained within this compartment, thereby limiting its exposure to parenchymal cells and mitigating its neurotoxic potential.

Disclosures: R. Tao: None. **G. Shim:** None. **G. Giordano:** None. **G. Chapagain:** None. **H. Prentice:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.12/W2

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

Support: NIH Grant U01NS114144-03S1

Title: Serum pTau217, total tau, GFAP and NF-L levels as a function of sex, race, age and comorbidities among community-dwelling U.S. adults

Authors: *C. DEMOS[1], B. NGO[1], J. ABRAHAM[1], C. CAMPBELL[1], D. ROBLIN[2], E. A. SHAMIM[2], G. SIGAL[1], J. WOHLSTADTER[1], M. STENGELIN[1];
[1]Meso Scale Diagnostics, LLC., Rockville, MD; [2]Mid-Atlantic Permanente Res. Inst., Washington, DC

Abstract: Tau (total), phosphorylated tau (pT217), glial fibrillary acidic protein (GFAP) and neurofilament light (NF-L) are useful biomarkers to detect neuropathologies. To better understand the influence of age, sex, race, and comorbidities on biomarker levels, we measured these proteins with Meso Scale Discovery (MSD) ultrasensitive S-PLEX immunoassays in nearly 4,000 samples among diverse, community-dwelling U.S. adults. Specimen records of Kaiser Permanente Research Biobank participants (>400,000) were linked with electronic medical records (EHR) for demographics and health history, including ICD9/ICD10 diagnosis codes. Eligible serum specimens were collected by the Biobank from 2010-2023 from individuals 40-89 years of age with no history of traumatic brain injury, stroke, brain tumors or other neurological disorders. To be included in the study as healthy controls (HC), individuals must not develop Alzheimer's Disease (AD), AD-related dementias (ADRD), or mild cognitive impairment (MCI) at any time in the follow-up period. HC were identified and stratified into groups defined by age in 10-year intervals, sex, and race. From each group, up to 125 patients were randomly selected (n=3,628). Comorbidities were identified from ICD9/ICD10 codes in the three years prior to collection. Samples were provided to MSD and blindly analyzed with the S-PLEX pTau217 assay and Neurology Panel 1. Associations of age, sex, and race with biomarker levels were analyzed by ANOVA then ANCOVA with age as a linear covariate. A secondary analysis was conducted to ascertain if comorbidities were associated with high outlier biomarker levels in the HC groups. Among controls, all biomarker levels increased significantly with age ($p \leq 0.05$), consistent with the broader literature showing robust age-related associations. Expected findings included significantly higher GFAP in females than males, lower NF-L in non-Hispanic (NH) Black males compared with Hispanic males, and in NH Black females compared with NH White females, and disproportionate enrichment of diabetes and circulatory disorders among controls with high outlier biomarker levels. A novel finding was a sex-specific race association for GFAP: Hispanic females had significantly lower GFAP than NH Black and NH White females, whereas no race association was observed among males. Total tau was significantly elevated in males within every racial group and pTau217 was significantly higher in males than females but was not significantly associated with race, adding to a contested literature on sex and race effects for these markers.

Disclosures: C. Demos: A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **B. Ngo:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Abraham:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **C. Campbell:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **D. Roblin:** A. Employment/Salary (full or part-time):; Kaiser Permanente Mid-Atlantic States. **E.A. Shamim:** A. Employment/Salary (full or part-time):; Kaiser Permanente Mid-Atlantic States. **G. Sigal:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC. **J. Wohlstadter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Meso Scale Diagnostics, LLC. **M. Stengelin:** A. Employment/Salary (full or part-time):; Meso Scale Diagnostics, LLC..

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.13/W3

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

Support: Elma Dill Russell Spencer Foundation
NIH Grant P51OD011133

Title: Serum biomarkers of aging and neurodegeneration in chimpanzees

Authors: K. WOLFORD[1], S. AMBAVARAM[1], S. J. SUKOFF RIZZO[2], ***K. A. PHILLIPS**[1]; [1]Trinity Univ., San Antonio, TX; [2]Dept. of Med., Univ. of Pittsburgh Sch. of Med., PITTSBURGH, PA

Abstract: Chimpanzees (*Pan troglodytes*) can develop Alzheimer's-like histopathology in the brain, characterized by astrogliosis, microglial activation, amyloid-beta plaques, and tau lesions. As chimpanzees share roughly 98-99% of their DNA sequence with humans, they provide a valuable translational model for human brain aging, including factors that may influence susceptibility to Alzheimer's disease and related dementias. Serum biomarkers translate microscopic brain pathology into measurable signals in the blood, providing a non-invasive means of detecting neuronal and glial injury and degeneration. Here we assessed serum levels of several brain biomarkers associated with aging and neurodegeneration from 114 adult and geriatric chimpanzees, including 70 females and 44 males, ranging in age from 10.0 to 49.2 years. The number of samples ranged from 1 to 5 for both males and females, resulting in 224 total samples (female mean = 2.0; male mean = 1.9). Samples were obtained from the Biomaterials Repository at the Southwest National Primate Research Center. Serum samples were analyzed via electrochemiluminescent assay using the MesoScale Discovery platform (Meso Scale Diagnostics, Rockville, Maryland) for GFAP, T-tau, NfL, p-Tau217, Aβ40 and Aβ42. Preliminary results indicate several biomarkers - glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), total tau (T-tau) - significantly increased with age. Taken together, these findings highlight the importance of chimpanzees as models for studying the origins and progression of neurodegenerative diseases and shared mechanisms of resilience and susceptibility to humans.

Disclosures: K. Wolford: None. **S. Ambavaram:** None. **S.J. Sukoff Rizzo:** None. **K.A. Phillips:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.14/W4

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

Support: Alzheimer's Association Bridge Funding Award

Title: Benchmarking CNS-Derived Extracellular Vesicle Biomarker Profiles in Matched Human Plasma and Saliva for Early Alzheimer's Disease Detection

Authors: *F. A. HADDADIN[1], L. M. LICATINI[2], L. LICATINI[2];
[1]Univ. of Southern California, Alzheimer's Therapeut. Res. Inst., San Diego, CA; [2]Keck Sch. of Med. at USC, Chula Vista, CA

Abstract: Blood-derived extracellular vesicles (EVs) from neurons and astrocytes carrying Alzheimer's disease (AD) biomarkers can predict AD progression from mild cognitive impairment (MCI); yet their potential in saliva remains largely unexplored. Saliva-derived extracellular vesicles (sEVs) are promising non-invasive biomarkers for AD and other age-related dementias (ADRD), but their use has been hindered by unstandardized protocols for saliva collection, storage, and isolation. Building on our prior work showing that key AD biomarkers, including Aβ40, Aβ42, and total tau, were detectable in central nervous system (CNS)-derived sEVs. This study aims to apply a newly optimized saliva EV isolation and concentration workflow and compare biomarker profiles between matched saliva and blood plasma samples. Using matched saliva and blood plasma samples from individuals in a longitudinal study, including healthy controls and individuals diagnosed with AD, we isolated saliva-derived EVs using IZON qEV Original 35 nm size-exclusion chromatography columns with an established 375 µL saliva sample volume. This workflow builds on a previous sEV isolation method that used a precipitation-based protocol with a 1 mL saliva input volume. We optimized the isolation protocol by reducing the saliva input volume to 375 µL and using IZON qEV size-exclusion chromatography to improve feasibility for limited-volume samples. IZON fractions containing EVs were collected, concentrated, and further enriched for neuron-, astrocyte-, and microglia-derived EV populations using magnetic bead immunocapture. Matched saliva EV and plasma EV samples will be analyzed using NULISAseq Neuro 220 Panel, to quantify AD-related biomarkers and inflammatory cytokines. We expect to identify biomarker differences between saliva-derived and plasma-derived EVs, as well as disease-state-associated differences between AD and healthy control participants. By comparing matched saliva and plasma biomarker profiles within the same individuals, this study will evaluate whether saliva-derived EVs can serve as a non-invasive biofluid for detecting AD-associated biomarker changes. As one of the first studies to characterize and compare saliva EVs with matched plasma EVs within the same individuals, this work establishes a robust methodological framework that may pave the way for using saliva-based biomarkers to predict progression from MCI to AD in future studies.

Disclosures: F.A. Haddadin: None. **L.M. Licatini:** None. **L. Licatini:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.15/W5

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

Support: 5R01AG072727-03
UND School of Medicine and Health Sciences

Title: Saliva Cytokine Concentrations as Potential Biomarkers of Alzheimer's Disease

Authors: *A. M. FLODEN[1], C. K. COMBS[2];
[1]Biomed. Sci., Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND; [2]Dept of Biomed. Sci., Univ. of North Dakota Sch. of Med., Grand Forks, ND

Abstract: Worldwide, approximately 55 million people are living with Alzheimer's disease (AD), and that number is expected to increase to 139 million by 2050. Sensitive and specific biomarkers for identifying early disease are, therefore, attractive to the field. Phospho-tau and amyloid beta (Aβ) protein levels in cerebrospinal fluid and serum have been proposed as indices supporting disease diagnosis. We hypothesized that saliva could also serve as a reliable source of biomarkers for disease assessment. Saliva collection is noninvasive and relatively inexpensive. Moreover, it contains numerous proteins. To characterize disease-related protein changes in saliva, we compared male and female AD and control saliva, as well as saliva collected from 12-month-old littermate control male and female C57BL/6 wild-type and App^{NL-G-F} mice. Amyloid beta (Aβ) levels were quantified in saliva using Quanterix Simoa, and cytokines were measured using a RayBiotech slide-based array. There were no significant differences in Aβ1-40 or Aβ1-42 levels between control and AD saliva samples for either sex. Wild-type and App^{NL-G-F} mice also had no significant differences in levels of either peptide. However, there were numerous disease-related changes in cytokine levels. Female App^{NL-G-F} mice demonstrated higher levels of IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17, IL-17F, IL-13, IFN-γ, TFGβ1, IL-21, and IL-22 compared to their wild type female controls. Female App^{NL-G-F} mice also had reduced levels of TNFSF11, Osteoactivin, and CRP. Far fewer changes were observed in males. Male App^{NL-G-F} mice had elevated levels of Osteoactivin and reduced levels of IL-2 compared with their respective wild-type male controls. In human male AD saliva, we observed significant elevations in IL-1α, IL-4, IL-12p70, MIP-3α, MMP-13, Osteopontin, and Rank compared to male control saliva. AD male saliva had lower levels of MIP-1α compared to male controls. However, female AD saliva had elevated levels of only IL-1α compared to their female controls. These data demonstrate several increases and decreases in saliva cytokine levels in AD, suggesting these differences may serve as biomarkers of disease in both human and mouse samples. However, understanding the sex- and species-specific cytokine changes will require further investigation.

Disclosures: A.M. Floden: None. **C.K. Combs:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.16/W6

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

Support: RF1 AG084134
RF1AG084134-01S1
L30AG089724
R01 AG49749
R56 AG074613

Title: Sex influence in the association between inflammation and pTau217 in participants with cardiovascular risk factors and at risk for Azheimer's disease

Authors: C. J. MCLOUTH[1], C. K. PHAN[1], D. MERCURIO[2], E. SMITH[3], D. R. BRITSCH[2], C. STUART[2], N. JEBET[3], J. TURCHAN-CHOLEWO[4], D. C. GERMAN[5], R. ZHANG[6], A. M. STOWE[7], ***J. LUTSHUMBA**[3];
[1]Biostatistics, [2]Neurosci., [3]Neurol., [4]Dept of Neurol., Univ. of Kentucky, Lexington, KY; [5]Psychiatry, U Texas Southwestern Med. Cntr., Dallas, TX; [6]Univ. of Texas Southwestern, Dallas, TX; [7]Neurol., Univ. of Kentucky Med. Ctr., Lexington, KY

Abstract: Both hypertension and hypercholesterolemia are highly associated with systemic immune cell regulation and inflammation. These factors increase the risk for Alzheimer's Disease (AD). The role of sex in systemic inflammation, specifically in patients with hypertension and hypercholesterolemia, in the development of AD remains unclear. Our goal was to determine whether sex plays a role in the relationship between inflammatory cytokines and AD biomarkers. We measured major inflammatory cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, TNF-α) and the AD biomarker pTau217 from plasma of participants from the 'risk reduction for Alzheimer's disease (rrAD) two-year clinical trial (NCT 02913664; completed Jan. 2022; n=513 total participants). rrAD participants were cognitively normal with a history of hypertension, hypercholesterolemia, and a family history of dementia or subjective memory complaints. Inflammatory cytokines were quantified via Meso Scale Discovery (MSD), and pTau217 was measured using Quanterix Simoa. Data were analyzed using linear models including the main effects of cytokine, age, sex, and higher-order interactions. We found a sex-based difference in inflammatory cytokines such that females had higher levels of IL-12p70 and IL-1β (p=0.0005, p=0.001, respectively). No other sex-based differences were found. We also found a nearly significant sex-based difference in the association between IFNγ and pTau217 (p=0.056). We further characterized this association for IFNγ's ability to predict pTau217 in both males and females, which was statistically significant for males (p=0.034) but not in females (p=0.666). Additionally, there was a sex-based difference in the association between IL12p70 and pTau217 (p=0.046), predominantly driven by females (p=0.062) and not males (p=0.293). There were no other sex-based differences in the relationship between inflammatory cytokines and pTau217.Conclusion: Sex appears to modify the relationship between systemic inflammation and AD-related pathology in cognitively normal adults with cardiovascular risk factors.

Specifically, there was an association between IFNγ and pTau217 in males but IL-12p70 and pTau217 in females. These findings suggest different sex-specific inflammatory pathways linked to AD pathology in cognitively normal adults at high risk for AD.

Disclosures: C.J. McLouth: None. **C.K. Phan:** None. **D. Mercurio:** None. **E. Smith:** None. **D.R. Britsch:** None. **C. Stuart:** None. **N. Jebet:** None. **J. Turchan-Cholewo:** None. **D.C. German:** None. **R. Zhang:** None. **A.M. Stowe:** None. **J. Lutshumba:** None.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.17/W7

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

Support: ADDF GR21242

Title: Comprehensive analysis of fluid biomarkers in active Alzheimer's disease clinical trials

Authors: *A. N. TSAO[1,2], A. M. L. OSSE[1,2], J. W. KINNEY[1,2], L. TORIO[1,2], J. FONSECA[3], J. L. CUMMINGS[1,2];
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia worldwide and currently affects over 55 million people. Therapeutic development has advanced considerably, with three disease targeting therapeutics (DTTs) receiving FDA approval in recent years, supported by the increasing use of AD biomarkers. Fluid biomarkers provide a cost efficient, less invasive, and more accessible alternative to imaging biomarkers and are increasingly integrated into clinical trials. With two blood-based biomarkers approved by the FDA for AD primary care assessment and diagnosis, understanding how fluid biomarkers are selected and deployed in AD clinical trials has become increasingly important. In this study, we evaluated the use of fluid biomarkers in active AD clinical trials, with particular focus on the relationship between therapeutic mechanism of action, biomarker selection, and context of use. Clinical trial data were exported from clinicaltrials.gov, including biomarkers for eligibility criteria and outcome measures. Therapeutic and biomarker information was curated, annotated, and analyzed by biomarker and clinical trial experts. On January 1, 2026, there were 192 active AD interventional trials, including 71 DTT-small molecule therapeutics and 64 DTT-biologics. Biomarkers were incorporated in 91% of DTT trials (57% for inclusion, 37% as primary outcomes). Fluid biomarkers were used for trial enrollment in 35% (47/134) of DTT trials, with the most common being Aβ42 in CSF. Fluid biomarkers were used as a primary outcome biomarker in 17% (23/134) of DTT trials with phosphorylated tau 217 in plasma being used most frequently. The

largest category of DTTs include therapeutics targeting amyloid-beta, inflammation, and tau. Biomarker usage varies across the mechanism of action categories, with inflammation targeting therapies demonstrating greater use of fluid biomarkers than other categories. This analysis provides a comprehensive evaluation of fluid biomarkers utilized in active AD DTT clinical trials, assessing the alignment between therapeutic mechanism, biomarker selection, and context of use. We explore the incorporation of fluid biomarkers in relation to specific trial characteristics, including repurposed drug trials and trial sponsors. These findings describe the current landscape, demonstrate their abilities to strengthen trial design, and inform decisions regarding biomarker selection in future trials.

Disclosures: A.N. Tsao: None. **A.M.L. Osse:** None. **J.W. Kinney:** F. Consulting Fees (e.g., advisory boards); Quanterix. **L. Torio:** None. **J. Fonseca:** None. **J.L. Cummings:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropsychiatric Inventory, Artery, Vaxxinity, Behrens, Alzheon, MedAvante-Prophase, Acumen. F. Consulting Fees (e.g., advisory boards); Acadia, Acumen, ALZpath, Annovis, Aprinola, Artery, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/egt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, Sinaptica, TrueBinding, Vaxxinity.

Poster

PSTR221: Alzheimer's Disease: Fluid Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR221.18/W8

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

Support: NHMRC grant

Title: Characterisation of neurofilament light chain by novel proteolytic cleavage pathway

Authors: *Z. AHMADI[1,2];
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Abstract: Zahra Ahmadi **Abstract**
Characterization of Neurofilament Light Chain Fragmentation by Novel Proteolytic Cleavage Pathways in Human Brain
Neurofilament light chain (NFL) is a neuron-specific cytoskeletal protein, widely used as biomarker of neuroaxonal injury. Elevated NFL concentrations have been reported in cerebrospinal fluid (CSF) and blood across numerous neurological disorders. However, the proteolytic processing of NFL within the human brain remains poorly characterized, limiting understanding of the origin of circulating NFL fragments.

To investigate endogenous NFL fragmentation, pooled post-mortem human brain homogenates from Alzheimer's disease (AD) cases were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blotting using NFL-specific antibodies. In parallel, in silico analysis of the NFL amino acid sequence was performed to identify potential cleavage sites for Enterokinase and Factor Xa and predict the molecular weights of resulting fragments. Western blot analysis identified five NFL-immunoreactive species in human brain homogenates, consisting of full-length NFL and four lower-molecular-weight fragments. The observed fragment pattern indicates that NFL exists in multiple forms within human brain tissue rather than exclusively as full-length protein. In silico digestion predicted multiple cleavage sites for both Enterokinase and Factor Xa and identified theoretical fragment profiles that overlapped with the molecular weight range of experimentally observed NFL species.
These findings demonstrate the presence of multiple NFL fragments in post-mortem human brain tissue. Enterokinase and Factor Xa are candidate proteases whose predicted cleavage products overlap with the molecular weight range of the observed NFL species. By identifying candidate proteolytic pathways associated with NFL fragmentation, this study contributes to a more mechanistic understanding of NFL biology and its application as a biomarker of neurodegeneration.
Conflict of interest: No conflict of interest to be declared.
Funding: Funding was acquired by NHMRC grant.

Disclosures: Z. Ahmadi: None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.01/W9

Topic: C.03. Parkinson’s Disease

Title: IND-ENABLING DEVELOPMENT OF AN ANTI-NITRATED ALPHA SYNUCLEIN ANTIBODY SUPPORTS NDC-0524 FOR CLINICAL DEVELOPMENT IN PARKINSON'S DISEASE

Authors: *I. GRISWOLD-PRENNER[1], S. WRIGHT[1], X. XU[1], A. ULUSOY[2], D. A. DI MONTE[2], F. KAYSER[1];
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Abstract: Multiple lines of evidence suggest that tyrosine nitration of alpha-synuclein promotes disease in Parkinson’s Disease (PD) models. An antibody has been developed that precisely targets nitrated alpha-synuclein (nSyn) with high affinity and specificity. The nSyn Ab significantly reduced synuclein pathology and demonstrated neuronal protection in PFF, AAV-Synuclein/Paraquat and in AAV-Synuclein/GBA Tg mouse models of spread. Based on this strong *in vivo* efficacy, we advanced the humanized, affinity matured nSyn Ab, NDC-0524, into

IND studies, enabling a First-in-Human (FIH) study. Clinical plans leverage a biomarker-enabled strategy to characterize NDC-0524's ability to engage the nSyn in CSF target and to provide SAA-based Proof-of-Mechanism (POM). Plans for a FIH Phase 1/2a trial include evaluation of the safety, tolerability, and immunogenicity of NDC-0524, its pharmacokinetic profile, target engagement and SAA-based POM. The consistent efficacy findings across multiple mouse models strongly support nSyn's role as a pathogenic subspecies driving aggregation and spread in models of PD, highlighting the potential of targeting nSyn as a therapeutic strategy in the clinic. To this end, we are advancing NDC-0524 into clinical studies.

Disclosures: I. Griswold-Prenner: A. Employment/Salary (full or part-time):; Nitrase Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nitrase Therapeutics, Inc. **S. Wright:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nitrase Therapeutics, Inc. **X. Xu:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nitrase Therapeutics, Inc.. **A. Ulusoy:** None. **D.A. Di Monte:** None. **F. Kayser:** A. Employment/Salary (full or part-time):; Nitrase Therapeutics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nitrase Therapeutics, Inc..

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.02/W10

Topic: C.03. Parkinson's Disease

Support: Core research grant from Science and Engineering Research Board (SERB), Government of India (CRG/2019/006028

Title: Recharging Dysfunctional Mitochondria: Mitochondria Targeted Nanoconjugates Protect Dopaminergic Neurons in Parkinsonian Models

Authors: *N. KEETHEDETH;
Inter Univ. Ctr. for Biomed. Res. and Super Specialty Hosp., Kottayam, India

Abstract: Mitochondrial dysfunction and oxidative stress are central to the pathogenesis of Parkinson's disease (PD), underscoring the need for mitochondria-targeted neuroprotective strategies. Here, we present a novel engineered nanocarrier, based on dendritic polyglycerol (PG) conjugated with triphenylphosphonium (TPP^+), referred to as MitoPG, for safe and efficient delivery of therapeutics to neuronal mitochondria. Optimization of the molecular weight of PG and the TPP density on the nanocarrier resulted in the MitoPG candidate with superior

mitochondrial localization, minimal cytotoxicity, and no detectable impairment of mitochondrial functions. The optimized MitoPG also retained high targeting efficiency even in the case of MPP^+-induced mitochondrial dysfunction and demonstrated excellent *in vitro* blood-brain barrier permeability. Using rotenone-exposed differentiated SH-SY5Y cells and MPTP-induced Parkinsonian C57BL/6 mice, we further examined the toxicity and neuroprotective effect of MitoPG-conjugated antioxidants, curcumin and quercetin. Conjugation preserved mitochondrial targeting, markedly attenuated mitochondrial oxidative stress, and improved neuronal viability. These MitoPG conjugated antioxidants showed enhanced aqueous solubility and superior *in vitro* neuroprotection compared to free antioxidants. *In vivo*, MitoPG alone showed no acute oral toxicity (LD_{50} 310 mg/kg), while MitoPG-curcumin significantly ameliorated neurobehavioral deficits, restored striatal dopamine levels, and reduced dopaminergic neuronal loss in the substantia nigra. To our knowledge, this is the first demonstration of a dendritic polymer-based nanocarrier that exhibits high mitochondrial localization with reduced toxicity while preserving the mitochondrial functions. These results highlight the utility of MitoPG-conjugated antioxidants as promising platforms for mitochondria-targeted therapy in PD and related neurodegenerative disorders.

Disclosures: N. Keethedeth: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Study was granted Indian Patent No: 582721 granted to Mahatma Gandhi University.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.03/W11

Topic: C.03. Parkinson’s Disease

Title: Behavioral Recovery and Dopaminergic Support Following Movement-Associated Stimulation of Mesenchymal-Derived Dopaminergic Cell Transplants in a Rat Model of Parkinson's Disease

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Abstract: Parkinson’s disease (PD) is characterized by the degeneration of nigrostriatal dopaminergic neurons, resulting in motor dysfunction including impaired coordination and bradykinesia. While stem cell transplantation is a promising therapeutic strategy, long-term functional integration of transplanted cells into host circuitry remains a major challenge.

Previous work from our laboratory showed that stimulating transplanted dopaminergic neuronal-like cells during movement seems to enhance behavioral recovery and graft functionality. Yet those explorations looked at limited behavioral repertoires over a 3-week period. The ongoing study investigates this Hebbian stimulation paradigm with mesenchymal-derived dopaminergic neuronal-like cell transplantations (MSCds) across a variety of behaviors and measures related dopaminergic responses across an extended 70-day period. MSCds stably expressed the luminopsin LMO3 and were differentiated to a dopaminergic phenotype prior to transplantation into the lesioned striatum. Animals received varying levels of coelenterazine (CTZ)-mediated stimulation during swimming pairings across the timeline. We assessed forelimb asymmetry during swimming, ladder rung walking, drag testing, and vibrissae-elicited forelimb placing during the interim. Drug-free neurochemical support is evaluated at the end using in vivo microdialysis, while histological analyses assess graft survival and host-graft integration through TH, GFP, PSD-95, and GFAP labeling. Preliminary findings indicate that transplanted animals receiving repeated movement-associated stimulation show trends toward improved limb-use symmetry and enhanced performance on fine motor tasks compared to lesion controls. It appears early histological observations show survival of transplanted cells within the dorsal striatum and evidence of host-graft synaptic interaction. Ongoing analyses will determine whether repeated stimulation enhances dopaminergic release capacity and long-term functional integration of transplanted cells. These findings support the potential of combining activity-dependent stimulation with stem cell transplantation to improve functional restoration in PD and may form the basis of a strategy that may help stabilize the effectiveness of clinical transplantation.

Disclosures: T.L. Cammarano: None. **H.D. Gerow:** None. **I.P. Walton:** None. **K. Zarkar:** None. **A. Flowers:** None. **R.E. Leyko:** None. **A.C. Reyes:** None. **A.N. Castiglione:** None. **M. Choudhury:** None. **K.A. Jenrow:** None. **E.D. Petersen:** None. **J. Rossignol:** None. **G.L. Dunbar:** None. **M.I. Sandstrom:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.05/W12

Topic: C.03. Parkinson’s Disease

Support: NIH T32 Predoctoral Training in Pharmacological Sciences (5T32GM133332)
NIH R35HL161177
NIH R01HL162787

Title: Novel ubiquinone-based nitroalkene inhibits ferroptosis in Parkinson's disease

Authors: *L. E. COOKE[1], M. MILLER[1], K. FARMER[2], E. N. ROCHA[2], R. DI MAIO[2], A. STRAUB[3], M. FAZZARI[4];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide and the number of people affected is expected to increase as the population continues to age. In the U.S.A. there are about 60,000 cases diagnosed each year with $14 billion in estimated healthcare costs. All available therapies alleviate only PD symptomology without targeting the primary cause-nigrostriatal neurodegeneration. The characteristic degeneration of nigrostriatal dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) in PD is linked with multiple pathogenic events, including oxidative stress, α-synuclein aggregation, mitochondrial dysfunction, and neuroinflammation. Recently, the efficacy of orally administered small molecule nitroalkene 10-nitro-oleic acid (10-NO_2-OA) in preventing key PD-related oxidative events has been shown in a well-established sub-acute rotenone model of PD in rats. Specifically, 10-NO_2-OA inhibits NADPH oxidase 2 (NOX2) and leucine-rich repeat kinase 2 (LRRK2) hyperactivation, microglial activation, oxidative stress, and α-synuclein-dependent mitochondrial import impairment. Recently, multiple studies have demonstrated the role of ferroptosis in PD. Ferroptosis is a regulated cell death triggered by iron accumulation, overproduction of reactive oxygen species (ROS), glutathione peroxidase 4 (GPX4) inhibition, and consequent phospholipid peroxidation. Herein, we report that a novel ubiquinone-based small molecule nitroalkene (CP-50) inhibits both rotenone-induced NOX2 and LRRK2 hyperactivity in an in vitro rotenone model of PD and crosses the blood-brain barrier after oral administration in mice and rats. Unlike the previously studied 10-NO_2-OA, CP-50 has shown anti-ferroptotic actions in N27-A rat dopaminergic neuronal cells following inhibition of GPX4, FSP, and/or DHODH. We predict that CP-50 is acting as a radical trapping antioxidant like the ferroptosis inhibitor ferrostatin but confers additional protection from the pathogenic mechanisms of PD given its antioxidative and electrophilic properties. Overall, our data suggest that CP-50 could promote additional neuroprotective responses than classical small molecule nitroalkenes, thus representing a more effective potential pharmacological strategy against PD.

Disclosures: L.E. Cooke: None. **M. Miller:** None. **K. Farmer:** None. **E.N. Rocha:** None. **R. Di Maio:** None. **A. Straub:** Other; Dr. Straub received research funds from Bayer Pharmaceuticals and has a financial interest in Creegh and Furanica Pharmaceuticals. **M. Fazzari:** Other; Dr. Fazzari has a financial interest in Creegh Pharmaceuticals..

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.06/W13

Topic: C.03. Parkinson's Disease

Title: Novel allosteric GCase modulator GT-04686 reduces neuropathology and improves motor and non-motor function in a preclinical model of GBA1 Parkinson's disease

Authors: *J. TAYLOR[1], A. TRAPERO[2], A. RUANO[2], J. CARRILLO[2], E. CUBERO[2], N. PÉREZ-CARMONA[2], A. M. GARCÍA-COLLAZO[2];
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Abstract: Impaired glucocerebrosidase (GCase) function appears to broadly contribute to Parkinson's disease (PD) pathogenesis, even in non-GBA1 mutation carriers, making the enhancement of its activity a promising therapeutic strategy. GT-02287, an allosteric GCase modulator developed using Gain Therapeutics' Magellan™ virtual screening platform, is currently in clinical development as a potential disease-modifying therapy for PD. When applying the Magellan™ platform several hit chemical series potentially acting as GCase modulators were identified. These structurally diverse chemical scaffolds were the starting point for medicinal chemistry optimization. GT-04686 belongs to a chemical series structurally distinct from GT-02287 identified in this process and was optimized for robust activity in *in vitro* and *in vivo* PD models. GT-04686 is an orally bioavailable, brain penetrant, novel small-molecule structurally targeted allosteric regulator of GCase for the treatment of Parkinson's disease. To model GBA1-PD, C57BL/6 mice were subjected on day 1 to an intra-striatal injection of alpha-synuclein preformed fibrils (PFFs) combined with a 28 days low-level chronic intraperitoneal administration of conduritol beta-epoxide (CBE), a covalent GCase inhibitor. In a delayed treatment paradigm, starting 8 days after the initial toxic insult, GT-04686 was administered orally once daily until day 28. Motor and non-motor function was tested in wire hang, beam walk, nesting, and olfactory tests. On the day of sacrifice, plasma and brain were collected for biomarker and neuropathology analysis. Delayed administration of GT-04686 in a mouse model of GBA1-Parkinson's disease (GBA1-PD) improved motor function and rescued nest-building performance, a complex behavior involving cognitive function, as well as showing an effect on olfactory deficit. We additionally show that these behavioral improvements correlated with modulation of several biomarkers of PD pathology. In conclusion, the development of a new chemical series of GCase modulators has yielded GT-04686, a novel compound ready for IND-enabling studies for the treatment of Parkinson's disease and potentially other conditions involving GCase deficiency.

Disclosures: J. Taylor: A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **A. Trapero:** None. **A. Ruano:** None. **J. Carrillo:** None. **E. Cubero:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **N. Pérez-Carmona:** None. **A.M. García-Collazo:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.07/W14

Topic: C.03. Parkinson's Disease

Title: The Role of Dopamine D1 Receptors in Dopamine Dysregulation Syndrome in a Bilateral 6-OHDA Lesion Rat Model of Parkinson's Disease

Authors: *L. SIMENS[1], G. NOONE[2], N. HAKIMZADEH[3], J. PARK[4], H. PRISINZANO[5], C. R. BISHOP[6];
[1]Binghamton Univ., Brooklyn, NY; [2]Binghamton Univ., Sayville, NY; [3]Dept. of Psychology and Behavioral Neurosci., Binghamton Univ., Binghamton, NY; [4]Binghamton Univ., Dix Hills, NY; [6]Psychology, [5]Binghamton Univ., Binghamton, NY

Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder characterized by dopamine (DA) loss in the nigrostriatal pathway, causing motor and non-motor dysfunction. Although DA replacement therapies, including DA receptor agonists and levodopa (L-DOPA), mitigate PD symptoms, chronic use can induce dyskinesia, impulse control disorders and DA dysregulation syndrome (DDS). DDS is marked by excessive medication use and driven by DA-dependent reward mechanisms within ascending DA pathways and purported actions at D1- and D2-receptor-expressing medium spiny neurons. Building on our findings that L-DOPA has reinforcing effects, the D1 receptor partial agonist SKF-38393 was assessed. Twenty male and 16 female Sprague Dawley rats received either a bilateral 6-hydroxydopamine (6-OHDA) or sham lesion to the medial forebrain bundle, or no surgical intervention. We hypothesized that bilateral 6-OHDA lesions would induce motor deficits, sub-chronic administration of SKF-38393 would induce dyskinesia, and reinforcing effects would be amplified by greater DA loss. Motor impairment was evaluated using forepaw adjusting steps (FAS) and rotarod. Dyskinesia severity was measured using abnormal involuntary movements (AIMs). Reinforcing effects were evaluated using conditioned place preference (CPP). Results showed reinforcing effects of SKF-38393 in sham- and 6-OHDA-lesioned rats, while the latter group also displayed mild dyskinesia indicating overlapping mechanisms of motor and reward pathways. Immunohistochemistry (IHC) is expected to reveal lesion-induced reductions in tyrosine hydroxylase (TH) within the substantia nigra (SN) and ventral tegmental area (VTA), and elevated FosB in dorsal and ventral striata that would implicate striatonigral pathway overactivity. These findings support D1 receptor-specific mechanisms underlying DDS and inform targeted therapeutic strategies for managing DDS in PD patients.

Disclosures: L. Simens: None. **G. Noone:** None. **N. Hakimzadeh:** None. **J. Park:** None. **H. Prisinzano:** None. **C.R. Bishop:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.08/W15

Topic: C.03. Parkinson's Disease

Support: Grant NS132060
Grant MH136164
Grant MH141461

Title: Investigating Metabotropic Glutamate Receptor 4/7 Heterodimers as a Novel Drug Target for Parkinson's Disease

Authors: *Y. NOH[1], A. FERRANTI[2], C. M. NISWENDER[2];
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Abstract: In Parkinson's disease (PD), degeneration of dopaminergic neurons in the substantia nigra pars compacta produces pathological dysregulation of glutamatergic and GABAergic transmission throughout basal ganglia circuits. Standard dopamine replacement therapies do not halt disease progression and can produce long-term motor complications, highlighting a need for non-dopaminergic treatments. Metabotropic glutamate receptor 4 ($mGlu_4$), a presynaptic G_i/G_o-coupled receptor enriched at striatopallidal and subthalamic nucleus synapses, is a promising drug target to correct the excitatory/inhibitory imbalance. $mGlu_4$ positive allosteric modulators (PAMs) show antiparkinsonian efficacy in preclinical models such as haloperidol-induced catalepsy (HIC), and one $mGlu_4$ PAM is currently in Phase II clinical trials for PD. Interestingly, $mGlu_4$ forms heterodimers with other mGlu receptor subtypes, raising the possibility that PAM effects may depend on specific receptor configurations. Here, we sought to characterize the molecular pharmacology of $mGlu_4$-containing heterodimers to investigate whether they contribute to the efficacy of $mGlu_4$ PAMs. Using chimeric mGlu receptor constructs with $GABA_B$ receptor C-termini to control dimer subunit composition at the cell surface of HEK293 cells, we examined $mGlu_{4/7}$ and $mGlu_{4/8}$ heterodimers relative to $mGlu_{4/4}$ homodimers. We assessed the ability of two $mGlu_4$ PAMs with antiparkinsonian efficacy to potentiate glutamate dose-responses at these dimers in a functional receptor activity assay. Notably, the potency of glutamate at $mGlu_{4/7}$ was significantly lower than $mGlu_{4/4}$ and $mGlu_{4/8}$ in these assays (pEC50: $mGlu_{4/7}$ 4.59±0.27; $mGlu_{4/4}$ 5.23±0.11; $mGlu_{4/8}$ 5.57±0.04; one-way ANOVA $F(2, 6)=26.48$, $p<0.01$; Tukey's post hoc: $mGlu_{4/7}$ vs. $mGlu_{4/4}$ $p<0.01$; $mGlu_{4/7}$ vs. $mGlu_{4/8}$ $p<0.001$; $N=3$). However, in the presence of $mGlu_4$ PAMs, glutamate potency was significantly greater at $mGlu_{4/7}$ than all other configurations (pEC50: $mGlu_{4/7}$ 6.98±0.11; $mGlu_{4/4}$ 6.34±0.06; $mGlu_{4/8}$ 6.63±0.06; one-way ANOVA $F(2, 6) =48.94$, $p<0.001$; Tukey's post hoc: $mGlu_{4/7}$ vs. $mGlu_{4/4}$ $p<0.001$; $mGlu_{4/7}$ vs. $mGlu_{4/8}$ $p<0.01$; $N=3$). These results suggest that $mGlu_{4/7}$ heterodimers may exhibit enhanced PAM sensitivity. We therefore hypothesize that $mGlu_{4/7}$ heterodimers underly the antiparkinsonian efficacy of $mGlu_4$ PAMs. Using these pharmacological tools with *Grm7* ($mGlu_7$) knockout mice in the HIC model, we are testing the *in vivo* behavioral relevance of these findings. Together, this work may elucidate the biological mechanisms of $mGlu_4$ PAM efficacy and guide the development of mGlu heterodimer-informed therapeutic strategies for PD.

Disclosures: Y. Noh: None. **A. Ferranti:** None. **C.M. Niswender:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APPELLO Pharmaceuticals.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.09/W16

Topic: C.03. Parkinson’s Disease

Support: Michael Guckavan Fellowship for Interdisciplinary Excellence, School of Science, Mathematics, and Technology, Mount St. Mary's University

Title: Investigating Vitamins C and E as Antioxidant Treatments Against Oxidative Stress in a C. elegans Model of Parkinson’s Disease

Authors: *A. G. MONAGHAN[1], K. E. STEPLER[2], A. J. KALLARACKAL[3];
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Abstract: Parkinson’s disease (PD) is a neurodegenerative disease that is caused by the loss of dopaminergic neurons and oxidative stress. This neurodegeneration primarily leads to tremors and mobility issues. Though symptoms can be treated with speech and physical therapy and dopamine-regulating medications, there is no cure for PD. Vitamin C’s antioxidant behavior can help to protect the mitochondrial membrane and maintain mitochondrial function, while vitamin E is protective of lipids under oxidative stress. In this work, we tested whether vitamin C and E improve movement in a C. elegans PD model. This study utilized the NL5901 C. elegans strain, which overexpresses alpha-synuclein, as a model for PD, alongside the N2 control strain. The worms were raised to the 6-day-old adult stage (1-week post-L4) on four media conditions: vitamin C, vitamin E, vitamin C and E, and control. Movement was measured using a thrashing assay; the number of thrashes was counted in a 60-second video in M9 buffer, across six trials. Across treatment groups, the N2 control strain consistently showed higher thrashing rates than the NL5901 PD model strain. In N2, all treatments slightly reduced movement compared to control plates, with the combined C&E treatment showing the greatest reduction. In contrast, for NL5901, all vitamin treatments improved movement relative to the untreated control, with vitamin E and the combination treatment being most effective. Variability (RSD) was generally higher in NL5901 than in N2. The data indicate that NL5901 worms consistently moved less than N2 worms across all conditions, consistent with a PD movement phenotype, and that individual vitamin treatment, particularly vitamin E, improved movement relative to controls. Currently, we are expanding this study to investigate the impact of the treatments on mitochondrial health by staining and imaging mitochondria using a confocal microscope. To fully evaluate the effects of vitamin E and C treatments, we will integrate the thrashing data with mitochondrial analyses and continued analysis of movement, allowing us to assess whether improvements in movement correlate with mitochondrial health. These low-cost supplements warrant further study as an accessible treatment option for PD.

Disclosures: A.G. Monaghan: None. **K.E. Stepler:** None. **A.J. Kallarackal:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.10/W17

Topic: C.03. Parkinson's Disease

Support: DBT GRANT BT/RLF/Re-entry/42/2016
ICMR SENIOR RESEARCH FELLOWSHIP
CSIR FOR FELLOWSHIP

Title: Pharmacological Activation of Transcription factor EB Restores Organelle Homeostasis and Protects Against Parkinsonian Neurodegeneration

Authors: *J. MOHAMED AMEER[1], S. NARUKKOTTIL[2], S. ASMI T[3], D. SANTHOSHKUMAR[4], G. CHANDRA[5];
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Abstract: Mitochondrial dysfunction and lysosomal impairment are two converging pathological features of Parkinson's disease (PD), yet the mechanistic link between these organellar deficits remains incompletely understood. Here, we investigated how chronic mitochondrial stress compromises lysosomal homeostasis and explored therapeutic strategies to restore mitochondrial-lysosomal communication. Differentiated SH-SY5Y neuroblastoma cells exposed chronically to 1-methyl-4-phenylpyridinium (MPP^+; 500 μM) exhibited pronounced mitochondrial fragmentation, excessive reactive oxygen species (ROS) generation, and progressive lysosomal dysfunction characterized by lysosomal alkalization, impaired cathepsin maturation, and disrupted proteostasis. Notably, these lysosomal abnormalities emerged only following chronic, but not acute, MPP^+ exposure, revealing a temporal threshold for stress-induced lysosomal collapse.Mechanistically, chronic mitochondrial stress promoted the formation of ROS-enriched mitochondrial-derived vesicles (MDVs) marked by TOMM20 that trafficked toward lysosomes. This vesicular communication was associated with reduced Parkin expression and accumulation of Sorting Nexin 9 (SNX9), identifying a Parkin-SNX9-dependent nanovesicle trafficking pathway that mediates mitochondrial-to-lysosomal stress signaling. Restoration of lysosomal function through overexpression of transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy, rescued lysosomal acidification, preserved mitochondrial integrity, and significantly attenuated MPP^+-induced neurotoxicity.Furthermore, we identified Withanolide A, a bioactive phytochemical derived from *Withania somnifera*, as a potent inducer of TFEB expression and nuclear translocation. Withanolide A restored mitochondrial-lysosomal homeostasis, enhanced lysosomal function, and mitigated mitochondrial stress-induced neuronal injury. Importantly, administration of

Withanolide A in a Parkinsonian animal model conferred significant neuroprotection, preserving dopaminergic neuronal integrity and ameliorating disease-associated neuropathological alterations. Collectively, our findings uncover a previously unrecognized Parkin-SNX9-mediated mechanism linking chronic mitochondrial stress to lysosomal dysfunction and establish TFEB activation by Withanolide A as a promising therapeutic strategy for restoring organellar homeostasis and counteracting neurodegeneration in Parkinson's disease.

Disclosures: J. Mohamed ameer: None. **S. Narukkottil:** None. **S. Asmi T:** None. **D. Santhoshkumar:** None. **G. Chandra:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.11/W18

Topic: C.03. Parkinson's Disease

Title: Efficacy of SUVN-N9503012, a Selective 5-HT1A Receptor Partial Agonist, Intended for the Treatment of L-Dopa induced dyskinesia

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Abstract: Levodopa-induced dyskinesia (LID) continues to be a major challenge in the long-term treatment of Parkinson's disease (PD), largely due to abnormal dopaminergic signalling and irregular dopamine release from serotonergic neurons. Recent studies have highlighted the role of serotonin 5-HT1A receptors in regulating these mechanisms. SUVN-N9503012 is a 5-HT1A partial agonist that may have potential in the treatment of LID. The in vitro affinity and functional activity of SUVN-N9503012 at human 5-HT1A receptors were evaluated using radioligand and cell-based reporter gene assays, respectively. The pharmacokinetics of SUVN-N9503012 were evaluated in rats. Receptor occupancy (RO) was carried out in Wistar rats to confirm target engagement. Following the development of LID, rats were treated with SUVN-N9503012. Microdialysis studies were carried out to evaluate the effect of SUVN-N9503012 on monoamine levels. For LID, male Wistar rats were treated with rotenone (2.5 mg/kg, i.p.) for nine consecutive days to induce Parkinsonian symptoms. Animals were trained to stay on the rotating rod in a rotarod apparatus prior to the initiation of disease induction to ensure stable baseline performance. Disease induction was confirmed through reduced motor coordination and increased catalepsy compared to baseline. After confirming PD-like deficits, levodopa (6 mg/kg, i.p.) along with benserazide (12.5 mg/kg, i.p.) was administered from Day 9 to Day 24. Repeated treatment produced progressive and stable abnormal involuntary movements (AIMs), quantified using standardized scoring of axial, limb, orofacial, and locomotor dyskinesias, indicating successful induction of a reproducible dyskinetic phenotype. SUVN-N9503012 showed potent in vitro activity and receptor occupancy at 5-HT1A receptors. SUVN-N9503012 reduced LID with

attenuation of axial, limb, orofacial, and locomotor dyskinesias. A significant and consistent increase in cortical dopamine levels was observed in microdialysis studies. Based on the above results, SUVN-N9503012 may be a promising therapeutic agent in the treatment of LID.

Disclosures: N. Ganuga: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd. **K. Rathod:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences, Ltd..

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.12/W19

Topic: C.03. Parkinson’s Disease

Support: PGI 24/B356
PGI 24/B361
PICT 2019-0480
PICT 2021-IA-00052
PICT 2020-1734
PIP 11220200101606CO

Title: Geraniol Protects Against Oxidative Stress and Promotes Proteostasis Through SKN-1/Nrf2 and DAF-16/FOXO Activation in Neurodegeneration Models

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Abstract: Neurodegenerative diseases are characterized by progressive neuronal dysfunction associated with oxidative stress, protein aggregation, and impaired proteostasis. In Parkinson’s disease, oxidative damage contributes to α-synuclein aggregation and neurodegeneration. Geraniol, a major constituent of several plant essential oils, has been reported to possess antioxidant properties; however, its mechanisms of action and neuroprotective potential remain incompletely understood.Using *Caenorhabditis elegans* as a model organism, we investigated the effects of geraniol on oxidative stress resistance and proteotoxicity. Geraniol significantly reduced intracellular reactive oxygen species levels and enhanced survival under oxidative stress conditions. Genetic analyses revealed that these protective effects require the conserved transcription factor SKN-1/Nrf2. In addition, geraniol promoted DAF-16/FOXO nuclear translocation, suggesting activation of complementary cytoprotective pathways.To evaluate its

effects on neurodegeneration, we examined geraniol in both muscular and neuronal α-synuclein models of Parkinson's disease. Geraniol reduced α-synuclein aggregation, improved locomotor performance, and preserved dopaminergic neuron morphology and function. Importantly, the beneficial effects of geraniol on Parkinson's disease-related phenotypes were abolished in daf-16 and skn-1 mutant backgrounds, demonstrating that both transcription factors are required for its neuroprotective activity.Finally, we investigated whether geraniol-mediated protection extends to other proteinopathies. In models of Huntington's disease and Alzheimer's disease expressing polyglutamine-expanded proteins or β-amyloid, respectively, geraniol also alleviated proteotoxic phenotypes.Together, these findings identify geraniol as a potent modulator of conserved stress-response and proteostasis pathways. By promoting SKN-1/Nrf2- and DAF-16/FOXO-dependent protective mechanisms, geraniol mitigates oxidative stress, protein aggregation, and neuronal dysfunction, supporting its potential as a candidate for the development of therapeutic strategies against neurodegenerative diseases.

Disclosures: S. Romussi: None. **D.H. Rayes:** None. **M.J. De Rosa:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.13/W20

Topic: C.03. Parkinson's Disease

Support: CSIR 09/1252(0001)/2019
Higher Education Department, Government of Kerala, IN

Title: Nanoformulated asiatic acid preserves mitochondrial-lysosomal homeostasis and dopaminergic integrity in experimental Parkinson's disease

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Abstract: Parkinson's disease (PD) is characterized by progressive degeneration of nigrostriatal dopaminergic neurons driven by oxidative stress, mitochondrial dysfunction and impaired autophagic- lysosomal pathways. Asiatic acid (AA), a pentacyclic triterpenoid from *Centella asiatica*, exhibits antioxidant, anti-inflammatory and autophagy modulating properties. However, its therapeutic application is limited by poor bioavailability and restricted intracellular delivery. In this study, we investigated the neuroprotective efficacy of poly (lactic-co-glycolic acid) (PLGA)-based nanoformulated AA (*nf*-AA) and AA-enriched extract (*nf*-EXT) in cellular and animal models of PD. In SH-SY5Y neurons exposed to MPP^+, pretreatment with *nf*-AA and *nf*-EXT significantly improved cell viability, attenuated intracellular and mitochondrial reactive oxygen species generation, restored mitochondrial membrane potential, and rescued tyrosine

hydroxylase (TH) and dopamine transporter (DAT) expression compared with unformulated counterparts. Cellular uptake studies demonstrated efficient neuronal internalization of PLGA nanoformulations. Pharmacological inhibition using chlorpromazine, nystatin and methyl-β-cyclodextrin revealed predominant uptake through clathrin-mediated endocytosis, supporting enhanced intracellular delivery of encapsulated therapeutics. Mechanistic investigations further revealed that AA mitigated MPP^+-induced lysosomal dysfunction and preserved mitochondrial homeostasis, as evidenced by restoration of LysoTracker and LysoSensor fluorescence profiles, reduction of mitochondrial superoxide generation, recovery of mitochondrial membrane potential, and normalization of MitoTracker fluorescence patterns. In MPTP induced PD mice, pretreatment with *nf*-AA and *nf*-EXT markedly improved motor performance in pole, rotarod, beam balance, and swim tests. Neurobehavioral recovery was accompanied by significant restoration of striatal dopamine levels and preservation of dopaminergic neurons, as demonstrated by recovery of TH and DAT expression in substantia nigra. Notably, nanoformulations consistently demonstrated superior neuroprotective efficacy compared with unformulated AA and extract treatments. These findings identify *nf*-AA as a promising multi-target neuroprotective strategy that enhances neuronal delivery, while preserving mitochondrial function, lysosomal homeostasis and dopaminergic integrity in Parkinsonian neurodegeneration.

Disclosures: C.V. Saji: None. **G. Chandra:** None. **K.P. Mohanakumar:** None. **R. Shenoi:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.14/W21

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01 NS122805
Mary Mack Estate Gift

Title: Dyskinesia induced by a dopamine 2 receptor-like agonist, but not a dopamine 1 receptor-like agonist, is blocked by sub-anesthetic ketamine

Authors: J. R. MEREDITH[1], R. PARMAR[2], E. G. E. SMITH[3], A. MALIK[3], M. J. BARTLETT[4], S. J. SHERMAN[3], *T. FALK[3];
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Abstract: Ketamine infusions are effective therapy for depression and chronic pain. Our prior preclinical data shows that low-dose ketamine treatment can attenuate development of L-DOPA-induced dyskinesia (LID) and reduce existing LID long-term. This long-term reduction was also seen in a Phase 1 clinical trial after 10-hour infusion. Ketamine is known to be a NMDA receptor antagonist and a positive allosteric modulator of opioid receptors. Prior work showed that a

highly selective NMDA receptor antagonist (MK-801) and a mu/delta opioid receptor agonist (MMP-2200) both had differential effects on LID elicited by either dopamine 1 receptor-like (D1R) or dopamine 2 receptor-like (D2R) specific agonists. Male Sprague-Dawley rats were unilaterally injected with 6-hydroxydopamine to create a hemi PD model (n=9/group). PD rats were primed with daily injections of L-DOPA (6 mg/kg, i.p.; with 14 mg/kg benserazide) for 21 days, then a stable baseline of DR1-like (SKF 81297; 0.8 mg/kg, s.c.) or DR2-like (0.2 mg/kg quinpirole, i.p.) dyskinesia was established. Abnormal involuntary movements (AIMs; limb, axial and orolingual) were measured by a blinded observer for 3 hrs. On Day 0 after 10-hr-treatment with vehicle or ketamine (20 mg/kg, i.p.) D2R-like AIMs were tested and the vehicle group had a mean AIMs score of 64 and the ketamine-treated group of 20 ($p<0.001$; Mann-Whitney tests corrected for multiple comparison). On days 4 and 7 after quinpirole treatment alone, the ketamine-treated rats still showed a 50% reduction in their AIMs compared to vehicle ($p<0.001$) indicating the long-term effect that was prior shown for LID rats is also present. In contrast to the D2R findings, ketamine treatment failed to produce a significant reduction in AIMs elicited by the D1R agonist. Mean AIMs scores for the ketamine-treated D1R group remained comparable to vehicle controls during the acute session and post-treatment days. Our results show that LID induced by a D2R-like agonist was acutely reduced by a low-dose ketamine treatment, and the reduction was still present at the end of the experiment 1-week after ketamine-treatment. The data show a contribution of the indirect striatopallidal pathway to the anti-dyskinetic effects of ketamine. And our findings reveal a clear divergence in ketamine's effects on striatal signaling, while D2R-mediated dyskinesia was significantly and persistently reduced, D1R-mediated dyskinesia remained unaffected. This suggests that the anti-dyskinetic profile of ketamine is specific to the indirect striatopallidal and not the direct striatonigral pathway and provides further support for the repurposing of sub-anesthetic ketamine for individuals with LID.

Disclosures: J.R. Meredith: None. **R. Parmar:** None. **E.G.E. Smith:** None. **A. Malik:** None. **M.J. Bartlett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MJB owns stock in PharmaTher Inc. **S.J. Sherman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SJS has a patent for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease, that was licensed to PharmaTher Inc. in October 2020. F. Consulting Fees (e.g., advisory boards); SJS has consulted for PharmaTher Inc. **T. Falk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TF has a patent for the use of ketamine as a novel treatment for levodopa-induced dyskinesia associated with Parkinson's disease, that was licensed to PharmaTher Inc. in October 2020. F. Consulting Fees (e.g., advisory boards); TF has consulted for PharmaTher Inc. and also received travel support in 2022.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.15/W22

Topic: C.03. Parkinson's Disease

Support: NIH R01 AG054533

Title: Evaluating the Impact of a Novel Beta-Adrenergic Receptor Ligand on Mood, Cognitive Function, and Neuroinflammation in a Mouse Model of Parkinson's Disease

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Abstract: The locus coeruleus (LC) noradrenergic (NE) system is essential for regulating brain function and is among the first areas to exhibit pathological changes in Parkinson's disease (PD) and other neurodegenerative disorders, including Alzheimer's disease (AD). The loss of LC neurons begins early in both AD and PD, occurring before significant damage to other brain regions, and is associated with a range of symptoms such as motor dysfunction, cognitive impairment, sleep disturbances, and autonomic dysfunction. Notably, the reduction in NE levels due to LC degeneration can lead to increased neuroinflammation, further intensifying these symptoms, particularly, since non-motor symptoms often resist conventional therapies. This study aims to utilize replacement therapy to restore the diminished β-adrenergic receptor (β-ADR) signaling through a novel small molecule developed in our laboratory, KSN18, thereby compensating for the reduced NE tone in the brain. Our previous research has focused on AD, showing that lower NE levels worsen behavioral deficits in paradigms assessing mood and cognitive function, neuroinflammation, and β-amyloid (Aβ) pathology. In contrast, administration of β-ADR agonists and NE restoration improved behaviors and mitigated Aβ pathology and neuroinflammation in transgenic AD mouse models. These findings highlight the crucial role of LC NE tone and β-ADR signaling in the pathophysiology of mood disorders and cognitive impairments related to neurodegenerative diseases. In this current study, we will expand upon these insights by first investigating the effects of KSN18, a novel β-ADR agonist, on normal behavioral functions associated with mood and cognitive domains in control mice. We will assess the impact of KSN18 on anxiety, depression, exploration of novel environments, social behavior, and learning and memory. Furthermore, we will utilize a well-established 6-OHDA PD model to evaluate how KSN18 influences behavioral deficits, neuroinflammation and neurodegeneration.

Disclosures: S. Shamloo: None. **B. Klein:** None. **N.L. Saw:** None. **R.K. Lam:** None. **E.B. Defensor:** None. **M. Shamloo:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.16/W23

Topic: C.03. Parkinson's Disease

Title: Computational discovery of tiliroside as a new candidate for Parkinson's disease targeting FAM171A2

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Abstract: FAM171A2 has emerged as a promising therapeutic target in Parkinson's disease (PD), as its blockade inhibits α-syn internalization in both *in vitro* and *in vivo* models. In this study, structure-based drug design strategy was employed to identify novel compounds targeting FAM171A2 for the treatment of Parkinson's disease. The three-dimensional (3D) structure of FAM171A2 was downloaded from AlphaFold database having an average predicted local distance difference test (pLDDT) score of 58.84. The N-terminal domain of the protein was retained, whereas the transmembrane (TM) helix and the disordered C-terminal domains were removed from the AlphaFold model. The structure was further refined through 50 ns molecular dynamics simulations using CHARMM36 forcefield. The MD simulation results showed an average RMSD value of 0.22 nm, indicating a well-equilibrated system. An average structure was calculated from 10-50 ns trajectory, which served as initial structure for further analysis. Ramachandran plot of the model indicated that 97% of the residues were located within the favored regions. The binding site of the FAM171A2 was predicted using CASTp program. Docking-based virtual screening was performed using the PyRx software with the natural compounds library obtained from the CSIR-Institute of Himalayan Bioresource Technology (IHBT). The reference compound, bemcentinib, exhibited a binding energy of -10.1 kcal/mol and a hydrogen bonding interaction with residue ASN105. The compound tiliroside demonstrated a better binding affinity score of -10.5 kcal/mol, outperforming the reference compound. In comparison to reference compound, tiliroside indicated superior molecular interactions with FAM171A2 forming hydrogen bonding with residues SER50, ARG186, PHE188, and PRO189. Tiliroside also formed a π-π stacking interaction with TYR123, π-anion interaction with GLU206, and a π-alkyl interaction with PRO209. Moreover, tiliroside exhibited van der Waals interactions with residues GLY51, LEU53, TRP92, ASN105, SER106, GLN182, GLN183, MET185, ALA187, ALA190, LEU192. Tiliroside has reported antioxidant, antiproliferating, and free radical scavenger activities and we are currently investigating its neuroprotective properties for neurodegenerative disorders. Overall, tiliroside is a promising binder of the FAM171A2 protein encouraging further investigation of its therapeutic potential through *in vitro* and i*n vivo* studies.

Disclosures: R. Kumar: None. **I. Thakur:** None. **A. Kumar:** None. **G. Thakur:** None. **X. Li:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.17/W24

Topic: C.03. Parkinson's Disease

Title: Systemic multiparatopic a-synuclein nanobodies reach the brain and engage intracellular pathological targets in a mouse model of Parkinson's disease

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Abstract: Alpha-synuclein (aSyn) aggregation is a hallmark of Parkinson's disease (PD). A major obstacle to antibody-based therapies targeting aSyn is the poor blood-brain barrier (BBB) penetrance of conventional immunoglobulins (IgG), which achieve brain access of less than 0.1% of the injected dose. Nanobodies (single-domain antibody fragments derived from camelid heavy-chain antibodies) offer unique properties that facilitate BBB crossing and access to intracellular compartments. Here we report the in vivo biodistribution and target engagement of QBBP1 and QBTP1 nanobodies in a preformed fibril (PFF) mouse model. Both were labelled with near-infrared fluorescent dyes or conjugated to nanogold and administered intraperitoneally in mice bearing unilateral intrastriatal PFF injections (4 months post-PFF). Brain access was quantified by *in vivo* imaging and deep-tissue clearing/immunofluorescence on whole-brain preparations. Target engagement was assessed by split-luciferase complementation (SmBiT-QBBP1/LgBiT-A53T-aSyn AAV model), bioluminescence imaging, and nanogold-electron microscopy. Biodistribution kinetics were characterised from 1 hour to 72 hours post-injection.Both QBBP1 and QBTP1 achieved brain penetrance of approximately 2.5% of the injected dose, representing a greater than 25-fold improvement over conventional IgG. *In vivo* imaging confirmed selective accumulation of nanobodies at sites of aSyn pathology in the injected hemisphere. Deep-clearing whole-brain immunofluorescence demonstrated co-localisation of nanobodies with phospho-Ser129-aSyn deposits and tyrosine hydroxylase-positive neurons. Electron microscopy with nanogold-labelled QBTP1 confirmed intracellular localisation of the nanobody within striatal and nigral neurons bearing PFF-induced inclusions. Split-luciferase complementation assays provided direct biochemical evidence of target engagement with pathological aSyn species *in vivo*. Parallel experiments are underway in a non-human primate PFF model (14 months post-PFF) to assess brain access and target engagement in a larger-brained species.These unique data establish that QBBP1 and QBTP1 cross the BBB after intravenous administration at concentrations far higher (x25) than those of conventional antibodies, reach the anatomical sites of aSyn pathology, and engage their targets intracellularly. These findings support the development of nanobody-based strategies as a viable therapeutic approach for synucleinopathies and provide the first quantitative *in vivo* evidence of intracellular aSyn target engagement by an intravenously delivered biologic in translational PD models.

Disclosures: C. mazzocco: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); QABY BIOTECH® LLC. **A. Mesleh:** None. **N. Vaikath:** None. **B.H. Bioulac:** None. **N. Majbour:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); QABY BIOTECH® LLC. **O. El-Agnaf:** E.

Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); QABY BIOTECH® LLC. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); QABY BIOTECH® LLC.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.18/W25

Topic: C.03. Parkinson's Disease

Support: NIH NINDS R01-NS110613
NIH NINDS R01-NS131371
NIH NINDS R01-NS058945
NIH NINDS R37-NS077657
NIH NINDS P50-NS123109

Title: Evaluating cortical beta as a biomarker for parkinsonian motor symptom severity

Authors: K. ACEDILLO[1], ***A. K. VERMA**[2], D. LEONARD[2], A. L. DENICOLA[1], J. WANG[1], J. L. VITEK, MD, PHD[3], L. A. JOHNSON[4];
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Abstract: Excessive beta (8-30 Hz) oscillatory activity in the subthalamic nucleus (STN) and internal globus pallidus (GPi) are recognized biomarkers for severity of Parkinson's disease (PD) motor signs, and is increasingly used as control signal for adaptive deep brain stimulation (DBS). Stimulation artifacts, however, limit the reliability of motor state determination via sensing at the DBS site (STN or GPi). The primary motor cortex (M1), a critical node in the basal ganglia-thalamocortical (BGTC) circuit, is postulated to exhibit abnormal signaling associated with PD pathology and is proposed as a potential alternative to STN and GPi for adaptive DBS. However, the relationship between cortical beta oscillatory activity and severity of PD motor signs is not well understood. The goal of this study is to examine the correlations between low-beta (8-20 Hz) and high-beta (21-30 Hz) oscillatory activity within critical nodal points of the BGTC circuit and the severity of parkinsonian motor signs (mUPDRS). Recordings of local field potentials (LFP) from the M1, STN, and GPi and assessment of motor symptom severity were performed in two parkinsonian nonhuman primates. These recordings were conducted at baseline, prior to the administration of L-dopa, and at sequential intervals following administration (10-min blocks were recorded at 10-mins post-administration and at 30-mins intervals up to 180 mins). Welch spectral analysis was performed on M1, STN, and GPi LFP activity (1s long epochs). Total power in the low-beta and high-beta bands was obtained for each block and correlated to corresponding mUPDRS. Consistent with the literature, we observed that low-beta power in the STN and GPi positively correlated with parkinsonian motor symptom severity in both subjects.

Correlation between cortical low-beta power and parkinsonian motor symptom severity was inconsistent across subjects. In contrast, cortical high-beta power was negatively correlated with parkinsonian motor symptom severity in both subjects. The polarity of STN and GPi high-beta power correlations with motor symptom severity was inconsistent across subjects. Our findings suggest that cortical high-beta power is a reliable marker of parkinsonian motor sign severity and could serve as a control signal to inform precise, symptom-specific DBS.

Disclosures: K. Acedillo: None. **A.K. Verma:** None. **D. Leonard:** None. **A.L. DeNicola:** None. **J. Wang:** None. **J.L. Vitek, MD, PhD:** F. Consulting Fees (e.g., advisory boards); J.L.V. serves as a consultant for Medtronic, Boston Scientific, and Abbott. He also serves on the Executive Advisory Board for Abbott and is a member of the scientific advisory board for Surgical Info. **L.A. Johnson:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.19/W26

Topic: C.03. Parkinson’s Disease

Support: PID2021-127800OA-I00
FI21/000919
MS19/00200
PI23/00496

Title: Non-invasive strategy to regulate neuromelanin accumulation by low intensity focused ultrasound in non-human primates

Authors: *N. ESTEBAN-GARCÍA[1,2], C. MARTÍN FLÓREZ[1,3], J. A. PINEDA-PARDO[1], M. LOPEZ-AGUIRRE[1], M. CARRILLO DÍAZ[4], R. RODRIGUEZ-ROJAS[1], I. TRIGO DAMAS[1], J. L. LANCIEGO[5], M. VILA[6], J. A. OBESO[1], J. BLESA[1];
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Abstract: Parkinson's disease is recognized by the gradual depletion of dopaminergic neurons containing neuromelanin, alongside an abnormal accumulation of iron within the substantia nigra pars compacta. Although existing treatments can alleviate motor symptoms, they fail to modify the course of the underlying neurodegeneration. Research suggests that when neuromelanin levels exceed a critical pathogenic threshold, they may induce cellular pathways fundamental to the development of Parkinson's. Low-intensity focused ultrasound paired with microbubbles (LIFU-MB) has emerged as a novel, non-invasive technique with the potential to modulate both

pigment concentration and protein clustering. In this study, we analysed the effects of LIFU-MB using a non-human primate model characterized by the continuous overexpression of human tyrosinase in dopaminergic cells, which causes a steady increase in neuromelanin. Detailed histological analyses were performed to determine neuromelanin density, determine neuronal integrity, identify intracellular deposits, monitor iron concentrations, and observe glial activity. The application of LIFU-MB result in a significant decrease in both intra- and extracellular neuromelanin, along with a downward trend in free ferric iron levels. Importantly, the intervention did not cause neuronal death or significant activation of astrocytes or microglia, confirming its safety. Collectively, these results suggest that LIFU-MB is a viable non-invasive method for regulating neuromelanin levels in vivo, emphasizing its promising value as an early-stage intervention for Parkinson's disease.

Disclosures: N. Esteban-García: None. **C. Martín Flórez:** None. **J.A. Pineda-Pardo:** None. **M. Lopez-Aguirre:** None. **M. Carrillo Díaz:** None. **R. Rodriguez-Rojas:** None. **I. Trigo Damas:** None. **J.L. Lanciego:** None. **M. Vila:** None. **J.A. Obeso:** None. **J. Blesa:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.20/W27

Topic: C.03. Parkinson’s Disease

Support: R01NS130551 (NIH/NINDS)
P51-OD011132 (NIH support to ENPRC)

Title: Behavioral effects of chemogenetic silencing of the internal globus pallidus in parkinsonian macaques

Authors: E. M. BOSSARD[1], D. PITTARD[1], X. HU[1], T. WICHMANN[1,2], *A. GALVAN[3,2]; [1]Neuropharm. and Neurologic Dis., Emory Natl. Primate Res. Center, Emory Univ., Atlanta, GA; [2]Neurol., Sch. of Medicine, Emory Univ., Atlanta, GA; [3]Emory Univ., Atlanta, GA

Abstract: Motor deficits in Parkinson’s disease are associated with abnormal neuronal activity in the basal ganglia. Lesions or deep brain stimulation targeting the internal globus pallidus (GPi), the main output nucleus of the basal ganglia, can effectively alleviate symptoms. However, these interventions are invasive and may produce serious side effects. Therefore, minimally invasive reversible and doseable approaches to alter GPi activity are needed. We are testing a chemogenetic strategy using chimeric ligand-gated ion channels to transiently inhibit GPi activity in parkinsonian monkeys. We expressed the inhibitory receptor PSAM4-GlyR in the GPi of two rhesus macaques (1 female, 1 male; 5-7 years) via injections of AAVdj-Syn-PSAM4-GlyR-m3m4-HA. The animals were trained on a touchscreen-based arm reaching task in which they had to touch and hold a center target until a second lateral target appeared. Touching the second target would then result in delivery of a food reward. After training, parkinsonism was

induced using weekly MPTP injections (0.2-0.8 mg/kg i.m.) until moderate symptoms developed. Chemogenetic modulation was accomplished by administering the PSAM agonist PSEM817 (0.1 mg/kg s.c.). L-DOPA (15-20 mg/kg, i.m.) administration served as a positive control, and i.m. or subcutaneous saline injections as a vehicle control. Behavioral outcomes were compared using independent-samples Kruskal-Wallis tests. Activation of PSAM4-GlyR with PSEM817 significantly reduced the movement time to reach the second target, compared to treatment with saline or with LDOPA ($p<0.001$, $\eta^2 = 0.02$) in both animals. The movement velocity was similarly increased after PSEM817 compared to the other treatments ($p<0.001$, $\eta^2 = 0.01$). In contrast, LDOPA significantly reduced reaction times ($p<0.001$, $\eta^2 = 0.11$), and increased movement amplitude ($p<0.001$, $\eta^2 = 0.05$). These experiments confirmed that the chosen chemogenetic approach exerts antiparkinsonian effects. The interesting differences between the antiparkinsonian effects of LDOPA and putative chemogenetic inhibition of GPi neurons could point to different networks resulting in parkinsonian bradykinesia and hypokinesia. The animals are currently undergoing tests of the effectiveness of the more easily available PSAM agonist varenicline, and assessments of the effects of chemogenetic activation on spontaneous locomotion.

Disclosures: E.M. Bossard: None. **D. Pittard:** None. **X. Hu:** None. **T. Wichmann:** None. **A. Galvan:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.21/W28

Topic: C.03. Parkinson’s Disease

Support: Secretariat of Science Humanities Technology and Innovation, Basic and Frontier Science program (CBF2023-2024-1888)

Title: Neuroprotective effect of the diterpene tilifodiolide in a murine model of parkinsonism

Authors: *A. ALONSO-CASTRO, A. MELECIO HERNÁNDEZ, M. GONZALEZ RIVERA, M. JUÁREZ VÁZQUEZ;
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Abstract: In our previous work, tilifodiolide (TDF), a diterpene isolated from Salvia tiliifolia, showed anxiolytic-like and antidepressant-like effects, with the possible participation of the gabaergic and adrenergic systems, respectively. This work used a mouse model of parkinsonism caused by the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to evaluate the neuroprotective effects of TDF. The Research Ethics Committee of the University of Guanajuato approved the protocol for this study (CIBIUG-P40-2021). Groups (n=8) of male C57BL/6 mice consisted of the following: a) Control: received oral saline for 28 days (total duration of the experiment). b) Vehicle: mice received five intraperitoneal (i.p.) administrations of MPTP (25

mg/kg) every 24 hours for five days. Then, the animals received oral saline for 23 days. c) Experimental groups received five administrations of MPTP (i.p.) every 24 hours for five days. These animals received TDF (0.1, 1, and 10 mg/kg p.o.) or L-Dopa (25 mg/kg p.o.) for 28 days, including intraperitoneal administration with MPTP. An additional group received only TDF (1 mg/kg p.o.) without MPTP. Each behavioral test (rotarod, catalepsy, and grip strength) was performed one hour after drug administration on days 17, 21, 24, and 28 of the experiment. The findings showed that the vehicle group (MPTP + saline) impaired ($p < 0.05$) the motor coordination of mice in the rotarod test at 0 h, 1 h, and 2 h, compared to the control group. TDF (0.1-10 mg/kg p.o.) maintained ($p < 0.05$) motor coordination in mice with parkinsonism, in a similar way to the control group, whereas the L-dopa + MPTP group decreased motor coordination ($p < 0.05$). The MPTP group showed a prolonged time of catalepsy, whereas the groups treated with MPTP + TDF (0.1-10 mg/kg p.o.) and MPTP + L-Dopa (25 mg/kg p.o.) exhibited a shorter ($p < 0.05$) catalepsy time with values close to the vehicle group. TDF (0.1-10 mg/kg p.o.) improved ($p < 0.05$) the grip strength time compared to the MPTP group, with similar activity to that shown by the control group. TDF (1 mg/kg) showed no alterations in locomotor activity, strength, or neurons positive to tyrosine hydroxylase (TH) in mice without parkinsonism. The MPTP group showed low positive neurons for tyrosine hydroxylase (TH), analyzed by immunohistochemistry, whereas the treatment with TDF (0.1 mg/kg p.o.) and L-dopa (25 mg/kg p.o.) increased the number of positive neurons for TH with similar levels to the control group. In conclusion, TDF (0.1-10 mg/kg p.o.) protected mice with MPTP-induced parkinsonism from motor coordination imbalance and strength loss by increasing the levels of TH in dopaminergic neurons.

Disclosures: A. Alonso-Castro: None. **A. Melecio Hernández:** None. **M. Gonzalez Rivera:** None. **M. Juárez Vázquez:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.22/W29

Topic: C.03. Parkinson’s Disease

Support: NIH Grant 2473702

Title: Chemical modulation of transplanted human mDA progenitors to accelerate the axon growth in a mouse Parkinson’s Disease model

Authors: *L. FENG[1], P. KANG[2], Y. TAO[4], S.-C. ZHANG[3];
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Abstract: Title: Chemical modulation of transplanted human mDA progenitors to accelerate the axon growth in a mouse Parkinson’s Disease model **Authors:** Li Feng, Philjun Kang, Yezheng

Tao, Suchun ZhangCenter for Neurologic Diseases, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037, USA **Abstract:** Parkinson's disease (PD) is caused by the loss of dopamine (DA) neurons in the midbrain. Current treatments, including L-dopa medication and deep brain stimulation, alleviate motor symptoms but do not stop the disease progression. Cell transplantation offers a promising way to replace lost DA neurons in the patient's brain. However, current transplantation strategies, including those in clinical trials, place cells in the striatum (ectopic) rather than substantia nigra (SN) of the midbrain (homotopic), functioning largely as a biological dopamine "pump" and thus providing only partial symptomatic relief. Such a strategy does not repair the nigra-striatal circuitry, and the DA release is not fully regulated, which may lead to side effects such as dyskinesia. We have shown that human stem cell-derived DA neurons, following transplantation into the SNc, project axons to the striatum, thus reconstructing the nigra-striatal circuitry and correcting motor deficits in PD mice. However, it takes 4~6 months to reconnect the nigra with the striatum of about 4~5 mm in mice. In humans, that distance is 45~50 mm with a 10-fold longer, implying that it would take up to 4 years for grafted neurons to extend axons to the target striatum. Consequently, this strategy is clinically less viable unless the axonal growth from grafted DA neurons is accelerated. In this study, we have explored accelerating the nigra-striatal circuit reconstruction by transplanting mDA neurons into the SN; the mDA neurons were generated from hiPSCs expressing DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). By administering Clozapine N-oxide (CNO) in the drinking water to activate grafted neurons, we observed earlier arrival of human axons in the striatum and corresponding behavioral recovery at 3 months post-transplantation (3 MPT), compared to the typical 6 months. We next aim to identify candidate genes and pathways underlying activity-dependent axon growth following DREADDs activation, with the goal of developing non-genetic approaches to promote axonal growth in the mature brain. Such activity-dependent axon growth represents a broadly applicable strategy for regenerative therapy. **Key words:**Midbrain dopaminergic neurons, Parkinson's disease, DREADDs, axonal growth

Disclosures: L. Feng: A. Employment/Salary (full or part-time):; Sanford Burnham Prebys Medical Discovery Institute. **P. Kang:** A. Employment/Salary (full or part-time):; Sanford Burnham Prebys Medical Discovery Institute. **Y. Tao:** None. **S. Zhang:** A. Employment/Salary (full or part-time):; Sanford Burnham Prebys Medical Discovery Institute.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.23/W30

Topic: C.03. Parkinson's Disease

Support: NIH R15NS133859

Title: Adaptive Optogenetic STN Stimulation Using Reinforcement Learning Improves Motor Behavior in Parkinsonian Rats

Authors: J. JACKSON, ***C. YU**;
Biomed. Engin., Michigan Technological Univ., Houghton, MI

Abstract: Deep brain stimulation (DBS) is an effective treatment for motor symptoms of Parkinson's disease (PD), but conventional continuous stimulation can be energy intensive and may contribute to cognitive and psychiatric side effects. Adaptive DBS (aDBS) has emerged as a promising strategy for improving PD treatment by adjusting stimulation based on ongoing neural activity. However, most existing aDBS systems rely on simple threshold-based control algorithms that do not adequately capture the temporal dynamics of pathological brain activity. In addition, neural recordings obtained during conventional electrical DBS are often contaminated by stimulation artifacts, limiting their suitability for closed-loop control. Here, we implement a reinforcement learning (RL)-based closed-loop neuromodulation framework combined with optogenetic stimulation of the subthalamic nucleus (STN) in 6-OHDA-lesioned female parkinsonian rats. Substantia nigra pars reticulata (SNr) beta-band activity (13-35 Hz) derived from spike recordings was used as the feedback signal for real-time control. A Deep Deterministic Policy Gradient framework was trained to suppress pathological beta activity by learning optimal stimulation policies from ongoing neural activity. Rather than responding to instantaneous beta power, the controller learned adaptive stimulation policies based on recent neural activity patterns. Across training, the controller exhibited progressive improvement in control performance, reflected in increasing cumulative reward and sustained suppression of beta-band activity. Following iterative training and optimization, the controller was deployed for real-time stimulation during behavioral testing. RL-driven optogenetic stimulation improved motor performance and reduced circling behavior comparable to conventional continuous 130-Hz DBS. These findings demonstrate the feasibility of combining optogenetics with reinforcement learning for real-time adaptive neuromodulation and establish a framework for developing intelligent closed-loop stimulation strategies for PD treatment.

Disclosures: J. Jackson: None. **C. Yu:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.24/X1

Topic: C.03. Parkinson’s Disease

Title: Noninvasive focused ultrasound-mediated AAV-facilitated gene therapy delivery to the mammalian brain: route- and species-dependent outcomes

Authors: *M. A. STAVARACHE, A. RAMOS, J. ROSENBERG, M. G. KAPLITT;
Neurosurg., Weill Cornell Med., New York, NY

Abstract: Focused ultrasound (FUS) combined with circulating inert-gas-filled microbubbles successfully opens the BBB transiently, locally, and reversibly, increasing the delivery of

therapeutic agents to specific brain regions. In this study, we assessed how the route of adeno-associated virus (AAV) administration affects the efficacy of targeted FUS-mediated gene delivery to rodent brains. Additionally, we demonstrated the feasibility of this approach to enhance gene therapy delivery to the brains of non-human primates (NHPs).AAV1/2-CAG-GFP, in combination with FUS targeting the striatum, was administered to Sprague-Dawley rats via either intra-arterial (IA) or intravenous (IV) routes at two AAV doses. To evaluate the clinical translatability, we combined magnetic resonance-guided FUS with IA (three NHPs) or IV (one NHP) AAV delivery in the putamen and hippocampus of African Green monkeys using clinically approved imaging, catheterization, and ultrasound systems. Two weeks post-sonication in the rodent studies and four weeks in the NHP studies, transgene expression, cellular tropism, and local inflammatory response were histologically assessed.In our study, the rodent data showed that IA administration of AAV achieved a significantly larger GFP transduction in the sonicated striatum than IV administration, independent of the AAV dose injected. No AAV dose- or route-dependent astrocytosis and microgliosis were observed.Our NHP data showed successful BBB opening in all targeted regions, confirmed by gadolinium extravasation on MR images acquired immediately after sonication. Immunohistological analysis of sonicated tissue revealed GFP-positive cells in the putamen of all subjects, regardless of AAV administration route. Analysis of the hippocampus identified GFP-positive cells only in one NHP from the IA delivery group and in the NHP that received AAV IV. These data suggest that FUS-mediated gene transduction in deeper brain regions might require further optimization of the acoustic pressure, AAV, and microbubble concentrations.Our findings demonstrate that IA administration substantially improves the efficiency of FUS-mediated AAV delivery in rodents under safe conditions. Furthermore, we provided the first demonstration of targeted gene delivery to the primate brain via IA administration, using exclusively clinically approved FUS, imaging, and catheterization technologies. Together, these results establish FUS-guided IA delivery as a clinically translatable strategy for safe, non-invasive, and dose-efficient gene therapy for Parkinson’s disease and other neurodegenerative disorders.

Disclosures: M.A. Stavarache: None. **A. Ramos:** None. **J. Rosenberg:** None. **M.G. Kaplitt:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.25/X2

Topic: C.03. Parkinson’s Disease

Support: Supported by UMB internal funding

Title: ProSAAS Preserves Nigrostriatal Dopamine Function in Both the 6-OHDA and alpha-Synuclein Rat Models of Parkinson's Disease

Authors: *I. GILDISH, C. F. CARDOZO HERNANDEZ, I. LINDBERG, J. F. CHEER; Dept. of Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Parkinson's disease (PD) is characterized by progressive degeneration of nigrostriatal dopaminergic pathway, resulting in impaired dopamine transmission and motor dysfunction. ProSAAS, a small chaperone protein, has emerged as a potential neuroprotective factor capable of reducing α-synuclein-caused dopaminergic degradation and motor impairment. This study evaluates the effects of proSAAS overexpression on dopamine signaling, motor behavior and dopaminergic terminal integrity in two different rat models of PD: the α-synuclein model and the 6-hydroxydopamine model. Adult male SD rats received bilateral dorsal-lateral striatal infusion of dopamine sensor GRABDA and photometry optic fibers and unilateral nigral administration of either 6-hydroxydopamine (6-OHDA) or AAV-mediated α-synuclein overexpression; and either lentiviral proSAAS or GFP (control) treatment. Dopaminergic dynamics were monitored using fiber photometry during operant behavioral testing. Motor performance was assessed using motor tests. Dopaminergic terminal integrity was evaluated using TH immunohistochemistry staining. Both 6-OHDA and α-synuclein expression produced a reduction in striatal dopamine signaling and motor performance. Lentiviral proSAAS administration attenuated these effects in both PD models. Fiber photometry recordings displayed partial preservation of dopamine-related signaling in proSAAS-treated animals as compared to GFP controls. Behavioral testing revealed improvements in selected motor tests following proSAAS expression. Histological analysis further demonstrated restoration of TH immunoreactivity in dorsal-lateral striatum of proSAAS-treated animals, suggesting at least partial preservation of the nigrostriatal dopaminergic pathway. This study provides preliminary results showing that proSAAS overexpression may mitigate dopaminergic dysfunction and motor impairment in both toxin and α-synuclein rat models of PD. These data support further investigation of proSAAS as a potential therapeutic strategy for Parkinson's disease.

Disclosures: I. Gildish: None. **C.F. Cardozo Hernandez:** None. **I. Lindberg:** None. **J.F. Cheer:** None.

Poster

PSTR222: Parkinson's Disease: Therapeutic Strategies in Preclinical Models

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR222.26/X3

Topic: C.03. Parkinson's Disease

Support: Key projects of National Natural Science Foundation of China（Grant No.82430045）
Key Research and Development Program of Zhejiang Province (Grant No. 2023C03079)

Title: The secondary motor cortex integrating visual-auditory inputs is critical to 40 Hz sensory stimulation alleviation of α-synuclein pathology

Authors: *J.-F. CHEN;
Eye Hospital;Wenzhou Med. Univ., Wenzhou, China

Abstract: Accumulation of pathologic α-synuclein (α-Syn) and progressive motor impairment are hallmarks of Parkinson's disease (PD), yet effective disease-modifying therapies remain lacking. Here we demonstrated that chronic (one-month) 40Hz audiovisual stimulation markedly reduced phosphorylated α-Syn (p-α-Syn) deposition, DNA damage, and apoptosis and rescued the impaired glymphatic inflow and outflow in TgM83 PD mice, while improving neuromuscular strength and motor coordination. Notably, these effects exhibited striking regional specificity: 40Hz stimulation selectively alleviated pathology in the motor cortex, but not other regions related to motor control or sensory perception. Importantly, we identified the most pronounced convergent projections from the primary visual cortex (V1) and auditory cortex (AC) to the secondary motor cortex (M2) (V1/AC→M2 pathway) that are rapidly and robustly engaged by 40Hz stimulation in wild-type mice but markedly attenuated in PD mice. Using second-generation targeted recombination in active populations (TRAP2) technology, we isolated 40Hz audiovisual stimulation-responsive neuronal ensembles (40Hz ensembles) in V1 and AC. Bidirectional optogenetic manipulations of the projection terminals in M2 from these 40Hz ensembles demonstrated that the V1/AC→M2 pathway was both necessary and sufficient for the 40Hz therapeutic effects. Specifically, optogenetic inhibition abolished, whereas optogenetic activation recapitulated the 40 Hz stimulation-induced reduction of p-α-Syn and restoration of motor function. Moreover, 40Hz stimulation enhanced aquaporin-4 (AQP4) expression and perivascular polarization in M2. 40Hz effect on AQP4 was abolished by optogenetic inhibition of V1/AC→M2 pathway and recapitulated by optogenetic activation of this pathway. Together, these findings delineated the V1/AC→M2 circuit- and the 40Hz-responsive ensembles as the critical substrate whereby non-invasive 40Hz sensory stimulation promoted α-Syn clearance and motor recovery through enhanced glymphatic function, establishing a mechanistic neural basis for 40Hz audiovisual stimulation as potential disease-modifying intervention for PD.

Disclosures: J. Chen: None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.01/X4

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

Title: Ethanolic Extracts of Halymenia durvillei Modulate JNK/NF-κB Signaling in Vascular Cognitive Impairment

Authors: *R. SUNAN[1,2], D. RODMA[1], S. CHOMPOOPONG[3];
[1]Mol. Medicine, Fac. of Sci., Mahidol Univ., Bangkok, Thailand; [2]Fac. of Allied Hlth. Sci.,

Pathumthani Univ., Pathum Thani, Thailand; [3]Dept. of Anatomy, Fac. of Med. Siriraj, Bangkok, Thailand

Abstract: Ethanolic extracts of marine red seaweeds, *Halymenia durvillei* (HDE) has previously been reported to be rich in fatty acids, particularly palmitic acid, which accounts for 79.65% of the total peak area composition as determined by Chromatography-Mass Spectrometry, and also included lipids, such as hexadecanoic acid, other phenolic compounds and bioactive secondary metabolites, which contribute to its pharmacological activity. HDE contains complex lipophilic compounds that may potentially inhibit the activity of secretory phospholipase A2 (sPLA2), a key enzyme responsible for producing pro-inflammatory lipid mediators like prostaglandins and leukotrienes in neuronal systems. In this study, HDE have been linked to the regulation of major intracellular inflammatory signaling pathways, including Mitogen-Activated Protein Kinases (MAPKs) such as JNK (c-Jun N-terminal kinases) and the NF-κB (nuclear factor kappa-B) pathway. Vascular cognitive impairment (VCI) was induced in adult male ICR mice with a modified bilateral common carotid artery occlusion (mBCCAO). Randomly treated groups received HDE (25 mg/kg, oral gavage, 28 days) or oleanolic acid (OA) as a standard positive control. HDE produced no detectable systemic toxicity. The results showed that HDE markedly reduced the overproduction of pro-inflammatory cytokines (TNF-α, IL-1β) and increased anti-inflammatory IL-10 ($p < 0.001$). HDE also significantly suppressed the expression of inducible nitric oxide synthase (iNOS) and reduced nitric oxide (NO) production ($p < 0.001$), both of which play pivotal roles in the inflammatory cascade. Moreover, in mBCCAO mice, HDE significantly attenuated neuronal loss in the hippocampal CA1 and CA3 regions and improved spatial learning and memory ($p < 0.001$). Reduced blood flow by arterial occlusion acts as a stressor that triggers JNK signaling and NF-κB activation, leading to white matter damage, microglial activation, and cognitive decline. JNK plays a key role in the disruption of the blood-brain barrier (BBB) following arterial occlusion and promotes neuronal apoptosis. The hypoperfusion could induce NF-κB, particularly in astrocytes and microglia, which results in the release of pro-inflammatory cytokines. These findings demonstrate that HDE mitigates neuroinflammatory cytokines and ameliorates VCI in mice, supporting its potential as a therapeutic candidate for neuroinflammatory and neurodegenerative disorders.

Disclosures: R. Sunan: None. **D. Rodma:** None. **S. Chompoopong:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.02/X5

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

Support: NSTC 113-2811-E-002-057-MY2

Title: Pomalidomide, an immunomodulatory imide drug (IMiD), alleviates iron imbalance-induced ferroptosis and minimizes neuroinflammation-mediated pyroptosis in the rat stroke models

Authors: *Y.-R. TSAI[1], Y.-H. CHIANG[2], A.-H. HUANG[3];
[1]Natl. Taiwan University, Col. of Med., Taipei City, Taiwan; [2]Taipei Med. Univ. Hosp., Taipei, Taiwan; [3]Natl. Taiwan Univ. Hosp. and Col. of Med., Taipei City, Taiwan

Abstract: Stroke is the leading cause of disability worldwide and the second leading cause of death, accounting for approximately 10 % of total deaths. Pharmacological approaches against ischemic stroke or hemorrhagic stroke remain limited, suggesting the need for a new therapeutic strategy. Pomalidomide, as an immunomodulator drug (IMiD), has been evaluated as a new treatment for neurological disorders with an inflammatory component. In this study, we use the rat 3-VO MCAo model, male SD rats, weighing 175-200g (n=4). Pomalidomide treatment is 20 mg/kg, IP injection at post-MCAo 0.5h. The rat collagenase-induced ICH model was used in male SD rats (n=4), weighing 250-300g. Pomalidomide treatment is 20 mg/kg, IP injection at post-MCAo 0.5h & 24h. And we analyzed the blood samples. In the MCAo model, the ferrous iron concentration showed in the pomalidomide treatment group was lower than in the vehicle group (mean 1.249 nM ± SEM 0.052 and 2.894 nM ±0.108, respectively). We also found the same tendency in the ICH model; the ICH with pomalidomide treatment group had lower ferrous iron concentration (0.144 nM ± 0.008 and 0.204 nM ± 0.031, respectively). With pomalidomide treatment, the downstream protein MDA was decreased compared to the vehicle group in the MACo model (mean 3.77 μM± SEM 1.14 and 7.86 ± 0.58, respectively) and the ICH model (mean 7.14 μM± SEM 0.5 and 13.87 ± 1.32, respectively). Meanwhile, we explored the levels of the neuroinflammation-mediated cytokines in the rat MCAo and ICH models. We found that pomalidomide treatment decreases the IL-1β versus vehicle treatment in the MCAo model (mean 22.82 pg/mL ± SEM 1.59 and 48.12 ±1.26, respectively) and in the ICH model (mean 56.51 pg/mL ± SEM 9.452 and 222.56 ± 2.27, respectively). The level of IL-18 in the MCAo model, pomalidomide treatment was left behind the vehicle group (mean 22.82 ng/mL ± SEM 1.59 and 48.12 ± 1.26, respectively), and the same result was achieved in the ICH model (181.814 ng/mL ± 8.71 and 532.73 ± 44.92, respectively). And the target protein, NLRP3-mediated pyroptosis, was significantly declined in the MCAo (mean 5.19 ng/mL ± SEM 0.2 and 8.75 ± 0.27, respectively) and ICH models (4.64 ng/mL ± 0.28 and 7.45 ± 0.53, respectively). To summarize, these findings certificated pomalidomide provides therapeutic targets for iron imbalance-induced ferroptosis and neuroinflammation-mediated pyroptosis in strokes.

Disclosures: Y. Tsai: None. **Y. Chiang:** None. **A. Huang:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.03/X6

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

Support: RS-2026-25482331

Title: Extracellular vesicles of Fusobacterium nucleatum induces anxiety and depression by triggering neuroinflammation via IL-1β activation

Authors: *C. CHUNG[1], Y. LEE[2], S.-Y. CHOI[3];
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Abstract: *Fusobacterium nucleatum* is an opportunistic Gram-negative oral pathogen capable of translocating to distant organs and eliciting inflammatory responses at sites of colonization. Extracellular vesicles derived from *F. nucleatum* (Fn EVs) have emerged as important mediators of inflammation in multiple organs, including the brain; however, their neuropathological effects remain poorly understood. In the present study, we investigated the impact of Fn EVs on the central nervous system through intracerebroventricular administration. Fn EV exposure induced pronounced neuroinflammatory responses, characterized by microglial activation and alterations in inhibitory synaptic transmission, which were accompanied by anxiety- and depression-like behaviors. Among the pro-inflammatory cytokines examined, IL-1β was selectively upregulated following Fn EV treatment. Notably, pharmacological inhibition of IL-1β signaling significantly attenuated the neuroinflammatory and behavioral abnormalities induced by Fn EVs. These findings demonstrate that Fn EVs promote neuroinflammation through an IL-1β-dependent mechanism, thereby contributing to anxiety- and depression-like phenotypes. Our study identifies Fn EVs as critical pathogenic mediators of oral microbiome-brain communication and suggests their potential involvement in the pathogenesis of neurological and psychiatric disorders.

Disclosures: C. Chung: None. **Y. Lee:** None. **S. Choi:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.04/X7

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

Support: This study is supported by a start-up fund from the Department of Biology at Syracuse University
This study is supported by a start-up fund from the Department of Biomedical and Chemical Engineering at Syracuse University

Title: A TNFR1-selective peptide allosteric inhibitor with blood-brain barrier-penetrating capability attenuates neuroinflammation and neurodegenerative pathology in a chronic inflammation mouse model

Authors: *Y. LIU[1,2], K. KALARY[2,3], X. CHEN[1,2], J. ZENG[1,2], C. LO[2,3];
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Abstract: A TNFR1-selective peptide allosteric inhibitor with blood-brain barrier-penetrating capability attenuates neuroinflammation and neurodegenerative pathology in a chronic inflammation mouse model

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Abstract

Neuroinflammation is a central driver of neurodegenerative diseases, including Alzheimer's and Parkinson's disease, contributing to blood-brain barrier (BBB) disruption, glial activation, and neuronal injury. Tumor necrosis factor (TNF) is a key mediator of these processes, largely through TNF receptor 1 (TNFR1), which drives pro-inflammatory signaling, barrier dysfunction, and cell death pathways. However, effective strategies to selectively suppress pathological TNFR1 signaling in the brain remain limited. Here, we evaluated FKC (FKCRRWQWRMKK), a TNFR1-selective allosteric inhibitory peptide, as a strategy to attenuate TNF-driven neurovascular and neurodegeneration-associated pathology. FKC binds an extracellular region of TNFR1 and stabilizes an inactive receptor conformation, thereby preventing formation of the TNF-induced signaling complex. In a human BBB-like transwell co-culture model (hCMEC/D3, hBVP, hAs), TNF reduced barrier integrity, increased permeability, and disrupted tight junction proteins (claudin-5, ZO-1, occludin). FKC preserved barrier function and tight junction organization. In human TNF transgenic mice, systemically administered FKC was detected in the brain, supporting its BBB-penetrating capability, and reduced neurovascular leakage, as indicated by decreased IgG and fibrin extravasation. FKC also preserved tight junction markers, reduced microglial and astrocyte activation, suppressed NF-κB signaling, and attenuated neuronal death-associated pathways, including necroptosis (MLKL/p-MLKL) and caspase-8 activation. Functionally, FKC improved spatial memory in human TNF transgenic mouse. Together, these findings support TNFR1 allosteric inhibition as a brain-accessible, receptor-selective strategy to interrupt the TNF-driven cascade linking BBB dysfunction, glial inflammation, and neuronal injury.

Disclosures: Y. Liu: None. **K. Kalary:** None. **X. Chen:** None. **J. Zeng:** None. **C. Lo:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.05/X8

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

Support: the Ministry of Science and Technology of China under grant numbers 2023YFC3603300
the Ministry of Science and Technology of China under grant numbers 2021ZD0200900
National Natural Science Foundation of China 32230049
National Natural Science Foundation of China 32341006
National Natural Science Foundation of China 32400785
National Natural Science Foundation of China 32541009

Title: A small molecule suppresses reactive astrocyte activity via TNFR2 adaptor-switching

Authors: *Y. GUO[1], J. ZHOU[2];
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Abstract: Neuroinflammation, primarily mediated by activated microglia and astrocytes, plays a pivotal role in the onset and progression of neurodegenerative diseases. Excessive astrocyte activation disrupts the homeostasis of the central nervous system (CNS). However, effective strategies to selectively limit maladaptive astrocyte responses while preserving their homeostatic functions remain scarce. Our previous study demonstrated that the astrocytic interaction between tumor necrosis factor receptor 2 (TNFR2) and regulator of G-protein signaling 5 (RGS5) enhances inflammatory astrocyte responses, thereby accelerating Parkinson's disease progression. Through a phenotypic screen targeting TNFR2-RGS5 axis-mediated inflammatory responses, we identify DAAP4, a novel small-molecular compound that selectively suppresses astrocyte-mediated neuroinflammatory responses by blocking TNFR2-RGS5 coupling. In mouse models of neuroinflammatory and neurodegenerative diseases, DAAP4 suppressed CNS inflammation with minimal effects on peripheral immune responses and attenuated disease progression in models of multiple sclerosis and Parkinson's disease. Mechanistically, DAAP4 prevented the enhanced coupling of TNFR2 with RGS5 in reactive astrocyte while preserving TNFR2-TRAF2-associated signaling, thereby suppressing maladaptive astrocyte responses while preserving homeostatic astrocyte phenotypes. Collectively, our findings identify DAAP4 as a selective modulator that restores balanced astrocytes by redirecting TNFR2 downstream signaling, offering a promising therapeutic avenue for neuroinflammatory CNS disorders and providing new insights into cell-type selective drug discovery.

Disclosures: Y. Guo: None. **J. Zhou:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.06/X9

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

Title: Integrated Plasma and CSF Biomarker Profiling Reveals Distinct Neuroinflammatory Signatures Across ALS and Multiple Sclerosis

Authors: C. J. MALTBY, J. PINTO, V. PERGHER, A. KELLERSOHN, E. PASCHEN, ***M. BIANCHI**;
Ulysses Neurosci. Ltd., Dublin, Ireland

Abstract: Background: Biomarker-driven clinical development is increasingly important for understanding disease mechanisms, validating therapeutic targets, and supporting patient stratification in neurodegenerative and neuromuscular disorders. Successful biomarker studies require integration of clinical operations, biofluid collection, sample processing, and robust analytical platforms. Here, we demonstrate an integrated translational biomarker framework through parallel plasma and cerebrospinal fluid (CSF) profiling in amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) cohorts. **Methods**: Studies were designed and executed in collaboration with San Raffaele Hospital (Milan, Italy), incorporating ethics approvals, patient recruitment, biobanking, and bioanalytical testing. Plasma and CSF were collected from ALS and MS patients and age- and sex-matched controls. Analyses used complementary Meso Scale Discovery (MSD) electrochemiluminescent ELISA and NULISAseq™ (Alamar) proteomic platforms, profiling Nf-L, GFAP, tau, phospho-tau isoforms, TDP-43, and inflammatory mediators of interferon signalling and innate immune activation. **Results**: Integrated plasma and CSF analyses identified robust disease-associated biomarker signatures. ALS samples showed significant alterations in markers of neuroaxonal degeneration and neuroinflammation, including Nf-L, GFAP, tau-related biomarkers, CCL2, CXCL10, and interferon-associated pathways. MS profiling identified distinct inflammatory and neurodegenerative signatures involving cytokine, chemokine, and glial networks. Compartment-specific plasma-CSF differences highlighted the value of multi-biofluid analyses, while strong MSD-NULISA concordance supported cross-platform analytical robustness. **Conclusions**: These studies demonstrate successful execution of end-to-end clinical biomarker programmes spanning partnerships, biofluid acquisition, biobanking, and multi-platform bioanalysis. Integrated MSD and NULISA profiling identified disease-relevant neurodegenerative and neuroimmune signatures across ALS and MS, providing analytical cross-validation between complementary technologies. This framework establishes a scalable translational strategy for biomarker discovery, target validation, patient stratification, and clinical development across neurological disorders.

Disclosures: C.J. Maltby: None. **J. Pinto:** None. **V. Pergher:** None. **A. Kellersohn:** None. **E. Paschen:** None. **M. Bianchi:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.07/X10

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

Title: FAAH Inhibition with URB-597 Attenuates Neuroinflammation-Induced Deficits in Working and Recognition Memory in Male Rats

Authors: *H. LOPEZ RIVERA[1], A. FRONTERA[2], C. MALDONADO IRIZARRY[3]; [1]Univ. de Puerto Rico - Rio Piedras, San Juan, PR; [2]Univ. of Puerto Rico Rio Piedras, San Juan, PR; [3]Univ. of Puerto Rico Dept. of Anat. & Neurobio. Grad. Program, San Juan, PR

Abstract: Neuroinflammation is a key component of cognitive decline, impairing learning, memory, and synaptic plasticity. Lipopolysaccharide (LPS) is widely used to model systemic inflammation, elevating pro-inflammatory cytokines that disrupt neuronal function. The endocannabinoid system (ECS), particularly anandamide (AEA), plays a crucial role in modulating stress responses and neuroprotection. Inhibiting fatty acid amide hydrolase (FAAH) with URB597 increases AEA availability and may attenuate neuroinflammatory effects; however, its impact on LPS-induced cognitive and structural deficits remains unclear. This study investigates whether FAAH inhibition can mitigate behavior. Male Sprague-Dawley rats (n=25) received LPS, URB597, or combined treatment for 21 days. Cognitive performance was assessed using Novel Object Recognition (NOR) for recognition memory and a T-maze spontaneous alternation task for working memory. Behavioral outputs were complemented by a computational multimodal model integrating behavioral metrics and inflammatory signatures to identify connectivity patterns predictive of cognitive impairment. LPS administration produced significant impairments in spontaneous alternation performance in the T-maze and reduced discrimination indices in NOR, consistent with inflammation-induced cognitive dysfunction. URB597 treatment attenuated these deficits, particularly in working memory performance, without fully restoring control levels. Behavioral tracking further revealed reduced locomotor activity and increased immobility in LPS-treated animals, partially normalized by FAAH inhibition. This study demonstrates that LPS administration induces robust impairments in both working and recognition memory in male rats, accompanied by behavioral patterns consistent with neuroinflammatory disruption. Inhibition of FAAH with URB-597 attenuated these cognitive deficits, particularly in spatial working memory. These findings support a modulatory and neuroprotective role of the endocannabinoid system in inflammation-related cognitive dysfunction. Furthermore, the integration of a computational behavioral analysis provided objective signatures of cognitive impairment, reinforcing the reliability of automated multimodal assessment in neuroinflammation models. Appreciation to Dr. Carmen Maldonado-Vlaar's mentorship throughout the development of this project, and the Julio García Díaz Biological Research Center for providing equipment and technical support.

Disclosures: H. Lopez Rivera: None. **A. Frontera:** None. **C. Maldonado Irizarry:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.08/X11

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

Support: NIH Grant R56AG079586

Title: Targeting pro-inflammatory effector iNOS improves cognitive and pathological deficits in an Alzheimer's disease mouse model

Authors: *M. GOVINDARAJAN[1], C. AWARE[1], K. IVANICH[1], N. BRESETTE[1], I. PATHAK[3], D. DAVIS[1], A. ERICSSON[1], L. MA[4], A.-L. LIN[2];
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Abstract: Introduction: Inflammation drives Alzheimer's disease (AD) pathogenesis, yet the direct effectors that connect systemic inflammation and neuroinflammation in AD are yet to be identified. Inducible Nitric Oxide Synthase (iNOS) is upregulated by pro-inflammatory signaling and may exacerbate AD pathology. To investigate this, we created a novel iNOS knockout (iNOS-KO/3xTg-AD) model using the 3xTg-AD mouse model background, to determine how iNOS-KO affects early cognitive, metabolic and pathological dysfunction. **Methods:** Y-Maze testing, glucose tolerance test (GTT), and immunohistochemical (IHC) analysis for phosphorylated tau (p-Tau) and a microglial marker (IBA1) were performed on iNOS-KO/3xTg-AD mice (n=9) and 3xTg-AD mice (n=10) at the 6-7-months age. Splenomegaly, an indicator of systemic inflammation in 3xTg-AD mice, was also assessed in a cohort of 12-13-month-old mice (n=4/age group). **Results:** iNOS-KO/3xTg-AD mice showed significantly improved spatial working memory compared to 3xTg-AD mice [Fig. 1(A)] in the Y-maze test. GTT revealed a trend of improved glucose tolerance in iNOS-KO/3xTg-AD mice [Fig. 1(C-D)], indicative of reduced AD-associated metabolic dysfunction. p-Tau burden was significantly reduced in iNOS-KO/3xTg-AD mouse brain [Fig. 1(H-J)], with no difference in IBA1 immunoreactivity, suggesting p-Tau reduction occurs independently of microglial abundance changes. Splenomegaly in the 12-13-month 3xTg-AD mice was significantly ameliorated by iNOS-KO [Fig 1(E-G)].**Conclusion:** iNOS-KO mitigates early cognitive deficits, phosphorylated-Tau pathology in the AD brain and glucose intolerance. Notably, p-Tau reduction occurred without changes in IBA1, highlighting a need to investigate the precise mechanism by which iNOS influences tau pathology. iNOS-KO also ameliorates splenomegaly, indicating its role as an effector at the center of systemic and neuronal inflammation contributing to AD. Collectively, these results show that targeting iNOS could mitigate early AD pathological onset in 3xTg-AD mice.

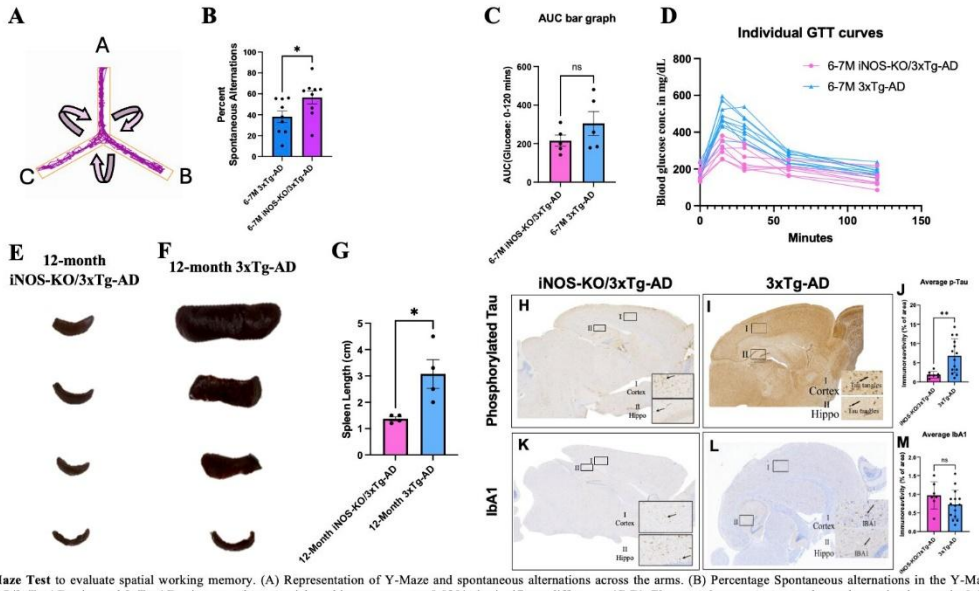


Fig. 1: (A-B) Y-Maze Test to evaluate spatial working memory. (A) Representation of Y-Maze and spontaneous alternations across the arms. (B) Percentage Spontaneous alternations in the Y-Maze test by the 6-7-month-old iNOS-KO/3xTg-AD mice and 3xTg-AD mice to evaluate spatial working memory. p =0.0201; *: significant difference. **(C-D) Glucose tolerance test** to evaluate glucose intolerance in 6–7-month-old iNOS-KO/3xTg-AD and 3xTg-AD mice. **(C)** Area Under the Curve (AUC) bar graph. Mann–Whitney test, $p > 0.05$; ns, not significant. **(D)** Representative curves of each mouse's glucose tolerance curve. **(E-G) Spleen size enlargement** was assessed in 12-month-old mice. Representative spleen images from (E) 12-month iNOS-KO/3xTg-AD mice and (F) 12-month 3xTg-AD mice. (G) Quantification of spleen length (cm). Mann-Whitney test, p = 0.0143, * significant. **(H-M) Immunohistochemistry (IHC)** for p-Tau and IBA1 in brain sections of 6-7-months-old 3xTg-AD and iNOS-KO/3xTg-AD mice. (A–B) Representative p-Tau images. (C) Quantification of p-Tau (% area immunoreactivity). (D–E) Representative IBA1 images. Mann–Whitney test, $p = 0.0028$; ** significant difference. (F) Quantification of IBA1 (% area immunoreactivity) in hippocampus and cortex. Mann–Whitney test, $p > 0.05$; ns, not significant.

Disclosures: M. Govindarajan: None. **C. Aware:** None. **K. Ivanich:** None. **N. Bresette:** None. **I. Pathak:** None. **D. Davis:** None. **A. Ericsson:** None. **L. Ma:** None. **A. Lin:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.09/X12

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

Title: Microglia-integrated human iCell NeuroSpheres for Neuroimmune modeling and translational biomarker assessment

Authors: *I. PEREZ-RUIZ, M. PENNAUER, I. SCHILCHER, T. LÖFFLER, M. PROKESCH;
Scantox Neuro GmbH, Grambach, Austria

Abstract: Human-relevant new approach methodologies (NAMs) are increasingly required to investigate mechanisms of neurodegeneration and improve translation between preclinical and clinical research. Three-dimensional (3D) neural spheroids provide a controlled multicellular environment that captures key cellular interactions while maintaining the reproducibility and scalability required for mechanistic studies and compound profiling. Here, we further qualified microglia-containing iCell NeuroSpheres to enable assessment of neuroinflammatory processes in brain region-specific models relevant to neurodegenerative disease. Forebrain and midbrain dopaminergic spheroids were generated from human induced pluripotent stem cell (iPSC)-

derived neural cells (FUJIFILM CDI) and combined with iPSC-derived GFP-expressing microglia using distinct integration paradigms. Microglial distribution and viability was assessed by confocal imaging, while inflammatory responsiveness, and translational biomarkers were evaluated using supernatant-based assays. Functional competence of integrated microglia was investigated following exposure to pro-inflammatory stimuli and disease-relevant lesions. Quantification of neurofilament light chain (NF-L), glial fibrillary acidic protein (GFAP), and inflammatory cytokines was performed using ELISA- and multiplex-based approaches. Microglia were successfully incorporated into both forebrain and midbrain dopaminergic neurospheres and remained functionally responsive within the 3D environment. Integration of microglia enabled interrogation of neuroimmune signaling while maintaining assay robustness and compatibility with scalable workflows. In addition, the model supported quantification of clinically relevant biomarker classes frequently used in translational neurodegeneration research. These results demonstrate the feasibility of incorporating human iPSC-derived microglia into iCell NeuroSpheres and expand the utility of this platform for investigating neuroinflammatory processes in neurodegenerative disease. The combination of cellular complexity, reproducibility, and scalability supports its application in mechanistic studies, biomarker evaluation, and compound screening.

Disclosures: I. Perez-Ruiz: A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Pennauer:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **I. Schilcher:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time):; Scantox Neuro GmbH.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.10/X13

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

Title: Development of a Human PSC-Derived Microglia-Neuron Co-Culture Platform for Modeling Neuroimmune Interactions

Authors: *A. MEKILE[1], C. STADLER[2], G. WONG[3], D. KUNINGER[1], **S. SHIN**[1]; [1]Thermo Fisher Scientific, Frederick, MD; [2]Thermo Fisher Scientific, Carlsbad, CA; [3]Thermo Fisher Scientific, San Diego, CA

Abstract: Microglia are central nervous system-resident immune cells that contribute to neurodevelopment, tissue homeostasis, synaptic regulation, and neurodegenerative disease. However, modeling human microglia function in vitro remains challenging because microglial identity and activity are strongly influenced by neuronal and environmental cues. To address this need, we are developing a human PSC-derived co-culture platform that combines PSC-derived neurons with fluorescently labeled induced microglia-like cells for visualization and assessment

of microglia-neuron interactions. Using a staged differentiation workflow, PSCs are first directed toward hematopoietic progenitors and subsequently matured toward an induced microglia-like phenotype under defined culture conditions. Fluorescent labeling of microglia enables their identification within mixed-cell cultures and supports live-cell imaging, cell tracking, and morphological assessment following introduction into PSC-derived neuronal cultures. This labeling strategy may be implemented through adding a fluorescent tag to an endogenous microglia associated loci by CRISPR/Cas9 or Viral vector, allowing flexibility depending on experimental requirements. The resulting co-culture model is designed to support evaluation of microglial survival, morphology, localization, and interaction with neuronal cultures, as well as future functional assays such as phagocytosis, inflammatory activation, cytokine release, and synapse-associated readouts. This platform enables a scalable human in vitro system for studying microglial behavior in a neuronal context and establishes a foundation for future disease-relevant applications in neurodegeneration and neuroinflammation.

Disclosures: A. Mekile: A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **C. Stadler:** A. Employment/Salary (full or part-time):; Thermo Fisher Scientific. **G. Wong:** 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):; Thermo Fisher Scientific.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.11/X14

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

Support: GliaCellTech Inc. 860-20230106

Title: Development of Recombinant Anti-TLR2 Antibodies and PLGA Nanoparticle-Based Gene Therapy for the Treatment of Neuropathic Pain

Authors: *S. LEE[1,2], E. BARCELON[1], J. HONG[2], S. LEE[3,2];
[1]Interdisciplinary Program in Neuroscience, Col. of Natural Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [2]OATC Res. Ctr. for Neurodiseases, Seoul, Korea, Republic of; [3]Dept. of Physiol. and Neurosci., Dent. Res. Institute, Seoul Natl. Univ. Sch. of Dent., Seoul, Korea, Republic of

Abstract: Neuroinflammation is a major contributor to neuropathic pain, and microglial Toll-like receptor 2 (TLR2) is an upstream mediator of nerve injury-induced inflammatory signaling in the spinal cord. However, antibody-based approaches targeting TLR2 are limited by poor central nervous system delivery and insufficient duration of action. In this study, we identified TLR2-targeting nanobody and single-chain variable fragment (scFv) candidates through phage display screening and developed a PLGA nanoparticle-based nonviral gene delivery strategy to

achieve sustained analgesia. The lead antibody fragments suppressed Pam3CSK4-induced TLR2/NF-kappaB activation and reduced proinflammatory cytokine expression in microglial and monocytic cells as well as in the mouse spinal cord. In adult male C57BL/6J mice, intrathecal administration of recombinant anti-TLR2 antibody fragments alleviated mechanical allodynia after peripheral nerve injury, with the lead candidates showing greater durability than a conventional anti-TLR2 antibody. To further prolong efficacy, plasmids encoding the selected nanobody or scFv were encapsulated in PLGA nanoparticles. A single intrathecal injection of antibody gene-loaded nanoparticles enabled sustained antibody expression in the lumbar spinal cord and produced sustained analgesia for up to 8 weeks after nerve injury. This treatment also attenuated spinal inflammatory mediator expression and shifted microglia and astrocytes toward less reactive morphologies. These results demonstrate that PLGA nanoparticle-mediated delivery of anti-TLR2 antibody genes can suppress glia-associated neuroinflammation and provide durable analgesia, supporting this platform as a potential therapeutic strategy for chronic pain driven by innate immune activation.

Disclosures: S. Lee: None. **E. Barcelon:** None. **J. Hong:** None. **S. Lee:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.12/X15

Topic: B.09. Glial Mechanisms

Title: Next-generation human iPSC-derived microglia for studying neuroinflammation and building complex 2D and 3D in vitro models for translational drug discovery

Authors: *R. NORTHEAST[1], P. BARTON[1], E. YATES[1], G. COOPER[2], E. JONES[3], M. TRIGANO[3], A.-N. MURGOCI[4], R. PRONK[5], P. SZESZULA[5], S. MILDE[2], R. HICKMAN[2], H. GARNETT[2], L. KOWALSKI[2], S. BARBARIA[6], C. SCHMIDT[6], S. SALIC-HAINZL[6], K. FIRTH[2], W. BERNARD[1];
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Abstract: Microglia act as the resident macrophages of the brain and are essential for neural homeostasis and responses to infection. Dysregulated microglial function is implicated in neurodegenerative diseases such Alzheimer's disease (AD), yet current in vitro models limit advances in drug discovery by failing to replicate cellular complexity and have poor reproducibility. Consequently, more advanced complex 2D and 3D in vitro models are required to better represent the in vivo environment and model neuroinflammatory processes for translational drug discovery.
To address this, we used opti-ox™, a deterministic cell programming technology, to generate scalable human-induced pluripotent stem cell (hiPSC)-derived ioMicroglia. These microglia

demonstrate high lot-to-lot consistency, express key microglia markers, and showcase robust functionality in phagocytic activity and secretion of pro-inflammatory cytokines upon stimulation with Amyloidβ1-42.
To advance AD and neuroinflammation modelling, we engineered ioMicroglia with relevant genetic mutations, such as TREM2 (R47H), APOE (C112R), and P2RY12 null/null, which are known to alter microglial function. These models exhibited expected phenotypic changes, including reduced phagocytosis in the TREM2 (R27H) lines, and ablated chemotaxis towards ATP in the P2RY12 null/null lines. Ongoing work includes assessment of lipid handling phenotypes in the APOE (C112R) line.
Complex 2D culture systems are important for high-throughput drug discovery. To support this we developed an optimised tri-culture protocol for ioMicroglia, ioAstrocytes, and ioGlutamatergic Neurons, and also showcase key microglia functionalities when in co-culture with neurons, including enhancement of neural network activity and the maintenance of phagocytic responses.
To support multicellular and 3D culture system development, we engineered GFP-expressing ioMicroglia. Here, we demonstrate the successful integration of these reporter microglia into a 3D bioprinting system, the Rastrum Allegro, and demonstrate a functional neuroinflammatory response to LPS, Amyloidβ1-42 and Nigericin treatment when in tri-culture with hiPSC-derived astrocytes and neurons. Furthermore, we demonstrate functional integration of ioMicroglia in a high throughput screening brain organoid model, and capture key neuroinflammatory signatures upon treatment with LPS which can be suppressed with dexamethasone.
In conclusion, our microglia models provide a physiologically relevant platform for investigating neuroinflammatory mechanisms and are amenable to 3D modelling, supporting critical advancements for drug discovery.

Disclosures: R. Northeast: A. Employment/Salary (full or part-time):; bit.bio. **P. Barton:** A. Employment/Salary (full or part-time):; bit.bio. **E. Yates:** A. Employment/Salary (full or part-time):; bit.bio. **G. Cooper:** A. Employment/Salary (full or part-time):; bit.bio. **E. Jones:** None. **M. Trigano:** None. **A. Murgoci:** A. Employment/Salary (full or part-time):; BrainZell. **R. Pronk:** A. Employment/Salary (full or part-time):; BrainZell. **P. Szeszula:** A. Employment/Salary (full or part-time):; BrainZell. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio. **R. Hickman:** A. Employment/Salary (full or part-time):; bit.bio. **H. Garnett:** A. Employment/Salary (full or part-time):; bit.bio. **L. Kowalski:** A. Employment/Salary (full or part-time):; bit.bio. **S. Barbaria:** A. Employment/Salary (full or part-time):; bit.bio Vienna. **C. Schmidt:** A. Employment/Salary (full or part-time):; bit.bio Vienna. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time):; bit.bio Vienna. **K. Firth:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.13/X16

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

Title: Neuroinflammation induction in iPSC-derived neuron-astrocyte-microglia tri-culture systems and its application to ASO toxicity assays

Authors: H. KOBAYASHI, H. MUNEZANE, ***S. ENDOH-YAMAGAMI**;
FUJIFILM Corp., Kanagawa, Japan

Abstract: Neuroinflammation is a protective immune response in the nervous system, but it also contributes to neurodegenerative diseases and the neurotoxicity of certain drugs, including antisense oligonucleotides (ASOs) administered via intrathecal injection. Therefore, modeling neuroinflammation is critical for both drug discovery and safety assessment.
Microglia play a central role in neuroinflammation; however, iPSC-derived microglia in monoculture typically exhibit an amoeboid morphology, indicative of an activated state. In contrast, we previously reported that microglia co-cultured with iPSC-derived neurons and astrocytes adopt a branched morphology resembling that of homeostatic microglia in vivo. Using this tri-culture system, lipopolysaccharide (LPS) stimulation elicited a robust neuroinflammatory response characterized by microglial morphological changes and induction of inflammatory cytokines.
Importantly, cytokine gene expression was not observed without microglia, indicating their essential role in initiating the response. Furthermore, cytokine release was significantly amplified in the tri-culture compared to the microglial monoculture. NF-κB nuclear translocation analysis revealed propagation of inflammatory signaling from microglia to astrocytes upon LPS stimulation. TNF-α antagonist treatment suppressed astrocyte activation without affecting microglia, suggesting that microglia-derived TNF-α drives secondary astrocyte activation, thereby amplifying neuroinflammation through intercellular interactions.
Given this amplified inflammatory response, we further evaluated whether this tri-culture system can detect neuroinflammation-related neurotoxicity of ASOs. We present findings from ASO treatment studies and discuss the utility of this platform for assessing neuroinflammatory susceptibility in drug development.

Disclosures: H. Kobayashi: A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **H. Munezane:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.14/X17

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

Support: Tufts Department of Biomedical Engineering Startup
NIH DP2NS140734-01

Title: Human pluripotent-stem cell derived microglia reveal sex-specific neuroinflammatory mechanisms relevant to pain

Authors: *L. A. MOSS, Z. LIAO, N. IYER;
Biomed. Engin., Tufts Univ., Medford, MA

Abstract: Sex differences in neuroinflammation remain poorly understood, limiting the development of effective chronic pain therapies. Recent evidence suggests that microglia, which are the resident immune cells of the central nervous system, modulate neuroinflammation in a sex-dependent manner, driving mechanical hypersensitivity in male but not female mice following nerve injury. Sex hormones may be contributing to these differences, as estrogen promotes an anti-inflammatory microglial phenotype, whereas testosterone drives autophagic activity. However, much of the evidence supporting these relationships derives from rodent models, limiting its translational relevance in humans. To combat this limitation, we are developing a novel human induced pluripotent stem cell (hiPSC)-derived microglial model using the KOLF2.1J CLYBL 6-TF-iMG KI1/KI2 line. Following the differentiation protocol by Dräger et al. microglia were differentiated in 10 days, with the differentiation efficiency confirmed by the generation of a 100% ionized calcium-binding adaptor molecule 1 (IBA1)-positive population. We hypothesize that estradiol and the androgen receptor agonist Cl-4AS-1 differentially modulate inflammatory and phagocytic microglial responses, thereby contributing to sex-specific pain susceptibility. In contrast to rodent studies identifying estrogen receptor β (ERβ) as the dominant estrogen receptor on microglia, we found that 100% of iPSC-derived IBA1+ microglia expressed estrogen receptor α (ERα), suggesting a different estrogen receptor expression profile in humans. Inflammatory and phagocytic gene expression are quantified by qPCR and analyzed by ANOVA, while changes in microglial morphology were assessed by immunocytochemistry using a custom-trained CellPose segmentation model. Our preliminary data demonstrate that hiPSC-derived microglia showed an upregulation of inflammatory marker IL6 and downregulation of homeostatic marker CX3CR1 in response to lipopolysaccharide (LPS) stimulation. This response was mediated by sex hormones in a dose-dependent manner, with 100pM of estradiol and 5uM of Cl-4AS-1 significantly reducing IL6 expression. Microglia will be co-cultured with dorsal spinal neurons derived from XX and XY iPSC lines to assess how hormone-dependent microglial activation influences neuronal function. These studies demonstrate, for the first time, that this cell line can be used to establish a human microglial platform for investigating sex-specific neuroimmune mechanisms that may contribute to sex-specific susceptibility to pain and other neuroinflammatory conditions.

Disclosures: L.A. Moss: None. **Z. Liao:** None. **N. Iyer:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.15/X18

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

Title: Integration of microglia into human brain organoids for modeling neuroinflammatory diseases

Authors: *A. LACROIX, N. COUNGERIS, V. ALSTAT, J. PERKINS, E. JOHNS, C. M. BUTT;
R&D, 28bio, Inc., Maple Grove, MN

Abstract: Neuroinflammation is a key component of many neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, and traumatic brain injury. We have already established a highly reproducible and scalable model of the human cerebral cortex (CNS-3D), but we have now improved it by incorporating isogenic microglia to make it immunocompetent. CNS-3D Inflammatory Organoids (CND-3D IO) were generated by adding microglia to CNS-3D derived from the same donor. Optimization studies determined the best conditions for microglia incorporation, including microglia density, culture media composition, and the age of CNS-3D at which microglia were added. Early integration at 2 weeks of maturation with ~10% microglia relative to the ~25,000 neurons and astrocytes present in CNS-3D organoids drove consistent incorporation, and supplementation with IL-34 enhanced microglia survival. The CNS-3D IO were then challenged with lipopolysaccharide (LPS) and tumor necrosis factor-α (TNF-α) and measured for cytokine profiling and immunocytochemistry. Stimulation with LPS or TNF-α both elicited robust cytokine release and imaging profiles consistent with neuroinflammation. Microglia were required for IL-1β, TNF-α, IL-10, and IL-6 responses to LPS. In addition, immunocytochemistry demonstrated that LPS stimulation shifted the morphology of the microglia from quiescent, sensing forms to activated states, while stimulation with TNF-α resulted in microglial migration. These findings support the use of CNS-3D IO as a high-throughput, human-relevant, screening tool for faster identification of clinical candidates that are targeted towards neuroinflammation and related neurodegenerative diseases.

Disclosures: A. LaCroix: A. Employment/Salary (full or part-time):; 28bio, Inc. **N. Coungeris:** A. Employment/Salary (full or part-time):; 28bio, Inc. **V. Alstat:** A. Employment/Salary (full or part-time):; 28bio, Inc. **J. Perkins:** A. Employment/Salary (full or part-time):; 28bio, Inc. **E. Johns:** A. Employment/Salary (full or part-time):; 28bio, Inc. **C.M. Butt:** A. Employment/Salary (full or part-time):; 28bio, Inc..

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.16/X19

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

Title: Integrating Microglia into Electrically Active iPSC-derived Neural Tri-cultures to Advance Neuroinflammation Studies

Authors: *C. B. CARLSON, R. FIENE, D. MAJEWSKI, M. DONEGAN, C. SAVIC, S. SCHACHTELE;
FUJIFILM CDI, Madison, WI

Abstract: Neuroinflammation is increasingly recognized as a central driver of virtually all neurological and psychiatric disorders, fueling a surge in research aimed at understanding its mechanisms and developing new therapeutic strategies. This growing focus has accelerated the development of complex, immune-competent human in vitro models that incorporate microglia, the resident immune cells of the brain. Access to human iPSC-derived neural cell types, combined with optimized physiological media and supplements, now enable creation of "brain-in-a-dish" model systems that support both functional neuronal activity and neuroinflammatory responses which more faithfully recapitulate the expected biology. In this study, we used cryopreserved cells available from FUJIFILM CDI to establish tri-cultures of human iPSC-derived neurons, astrocytes, and microglia, and systematically optimized conditions to generate electrically active, immune-competent models. We evaluated plating sequence, media, supplements, inflammatory stimuli, and 2D versus 3D formats across multiple assay endpoints. The results were compared to responses obtained with mono-cultures. Importantly, iPSC-derived microglia constitutively expressing GFP were used to facilitate identification of microglia survival, morphology, and incorporation/infiltration in these multivariable experiments. Neural activity was confirmed by calcium oscillation (FDSS or FLIPR) and multi-electrode array (Axion Maestro or Maxwell HD-MEA) assays. Tri-culture conditions with microglia clearly impacted spike activity and network bursting dynamics, but they also challenged the current analysis paradigms and highlighted the need for more advanced metrics. Cytokine release assay focused on canonical molecules like CCL2, IL-6, and TNF-alpha; as well as the NLRP3 inflammasome-related readouts IL-1beta and IL-18, which require nigericin to trigger maturation and release. Importantly, all of the assay readouts were useful in disease modeling studies with iPSC-derived microglia harboring mutations in the Alzheimer's Disease risk associated genes TREM2 and APOE. In summary, the experiments performed here support the electrophysiological activity of neurons (including glutamatergic, GABAergic, dopaminergic, and motor neurons), and have enabled the generation of new advanced methodologies (NAMs) in 2D and 3D capable of evaluating the functional impact of microglia and neuroinflammation in the context of various disease states.

Disclosures: C.B. Carlson: A. Employment/Salary (full or part-time):; FUJIFILM CDI. **R. Fiene:** A. Employment/Salary (full or part-time):; FUJIFILM CDI. **D. Majewski:** A. Employment/Salary (full or part-time):; FUJIFILM CDI. **M. Donegan:** A. Employment/Salary (full or part-time):; FUJIFILM CDI. **C. Savic:** A. Employment/Salary (full or part-time):; FUJIFILM CDI. **S. Schachtele:** A. Employment/Salary (full or part-time):; FUJIFILM CDI.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.17/X20

Topic: B.09. Glial Mechanisms

Title: Development of an iPSC-Derived Microglia/RPE coculture system to model retinal inflammation

Authors: M. DUBAUT, K. GILLOIS, A. HAGIMONT, Y. GRIMA, S. HUMPHREYS, ***D. WALLBANK**, B. ONTENIENTE, F. REGENT;
Axol Biosci., Cambridge, United Kingdom

Abstract: The retina is a specialized region of the central nervous system that converts light stimuli into electrical signals interpreted by the brain. One of the leading causes of retinal degeneration and vision loss is the Age-related macular degeneration (AMD). The cell type primarily affected in AMD is the retinal pigment epithelium (RPE), a specialized epithelial monolayer essential for the survival and function of photoreceptors (PRs), the sensory neurons of the retina. RPE atrophy in AMD is driven by multiple mechanisms, including chronic inflammation. Microglia, the resident immune cells of the retina, play a key role in regulating inflammation. Under physiological conditions, they reside mainly in the inner retina but become activated during degeneration, proliferating and migrating toward the outer retina where photoreceptors and RPE are located. Their role in AMD is not completely understood. They may initially clear debris but later contribute to disease progression by sustaining a chronic pro-inflammatory environment. Progress in understanding microglial involvement in AMD, and development of therapeutic strategies, has been hindered by the lack of in vitro models that faithfully recapitulate interactions between microglia and other retinal cell types, limiting retinal inflammation modelling. Here, we describe an induced pluripotent stem cell (iPSC)-derived RPE/microglia co-culture system to model retinal inflammation. Both cell types displayed typical morphology and expressed lineage-specific markers. RPE cells demonstrated key functions, including phagocytosis of photoreceptor outer segments and formation of a tight epithelial barrier. Microglial cells also exhibited key functions, including phagocytosis, activation by pro-inflammatory stimuli, and chemotaxis toward C5a. After establishing optimal co-culture conditions, we introduced A2E, a bisretinoid accumulating in aging RPE, as a stressor. Stressed RPE cells induced microglial activation, characterized by increased proliferation and inflammatory cytokine secretion. Additionally, RPE cells displayed increased sensitivity to A2E- and blue light-induced stress in co-culture compared to monoculture, highlighting inflammatory crosstalk. This model, in addition to representing an interesting platform to assess the efficacy of potential AMD treatments targeting retinal inflammation, highlights the potential of iPSC-derived microglial cells to model neuroinflammation. Consequently, Axol Bioscience is now developing additional co-culture models between microglia and other neuronal cell types, including cortical neurons.

Disclosures: M. Dubaut: A. Employment/Salary (full or part-time):; Axol Biosciences. **K. Gillois:** A. Employment/Salary (full or part-time):; Axol Biosciences. **A. Hagimont:** A. Employment/Salary (full or part-time):; Axol Biosciences. **Y. Grima:** A. Employment/Salary (full or part-time):; Axol Biosciences. **S. Humphreys:** A. Employment/Salary (full or part-time):; Axol Biosciences. **D. Wallbank:** A. Employment/Salary (full or part-time):; Axol Biosciences. **B. Onteniente:** A. Employment/Salary (full or part-time):; Axol Biosciences. **F. Regent:** A. Employment/Salary (full or part-time):; Axol Biosciences.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.18/X21

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

Support: CEA
Agence Innovation Défense

Title: Inflammasome activation drives DDX5-dependent ribosomal stress and translational dysfunction in an autologous neurovascular immune human organoid model of neuroinflammation, rescued by BRT_002

Authors: *N. METIVET[1], R. HARATI[2], A. BOUZID[2], N. COSTA[3], C. DISDIER[4], A. MABONDZO[5];
[1]CEA, Saclay, France; [2]Univ. of Sharjah, Sharjah, United Arab Emirates; [3]DMTS, CEA Saclay, Joliot Institute, DMTS, Paris Saclay Univ., Gif Sur Yvette Cedex, France, NOZAY, France; [4]CEA, DMTS, SPI, Neurovascular Unit Res. & Therapeut. Innovation Laboratory, Paris-Saclay Univ., gif sur yvettes, France; [5]CEA Saclay, Joliot Institute, DMTS, Paris Saclay Univ., Gif Sur Yvette Cedex, France

Abstract: Neuroinflammation is a major cause of acute brain dysfunction, yet the integrated neuroimmune and translational mechanisms driving neuronal vulnerability remain poorly understood in human systems. We establish an autologous human neurovascular immune brain organoid (BO) platform that recapitulates key features of inflammatory stress in a physiologically relevant context. We developed a human iPSC-derived BO platform across four conditions: non-vascularized, non-immunocompetent control, vascularized (Va), immunocompetent (Im), and vascularized immunocompetent (ImVa) BOs. Immunofluorescence and analysis at the transcriptional level confirmed co-existence of neural progenitors, mature neurons, astrocytes, oligodendrocytes, endothelial and microglia-like cells. Deep proteomic and network analyses highlighted 1,363 differentially expressed proteins (DEPs) comparing Im vs ImVa BOs. Among DEPs, we identified modulation in the vascularization-driven neuronal and glial maturation program (NEFL, NEFM, VGF, S100β) as well as a previously unrecognized DDX5 centered ribosome-translation axis, driving ribosomal stress and global translational dysfunction. LPS (100ng/mL, 24h)-induced inflammasome activation triggers a coordinated neuroimmune response characterized by cytokine synthesis (e.g., IL-1β, IL-6) and remodeling of cellular homeostasis. We validated that upon LPS stimulation ImVa BOs exhibit microglial activation (AIF1, C1QA/B/C, CASP1/4), endothelial dysfunction (ICAM1, VCAM1, MMP9, TGFβ1), oxidative stress (HMOX1, NQO1), astrocytic reactivity (GFAP, S100β), proteostatic stress (CALR) and suppression of progenitor markers (HMGA2, SOX2). In addition, DDX5 network collapsed in this neuroinflammatory context, including inhibition of ribosomal biogenesis (RPL/RPS), chromatin remodeling (PHC1, HMGN1, RYBP) and splicing (NSRP1, BUD13), directly antagonizing the vascularization-driven maturation program. BRT_002, a purine derivative and anti-inflammatory drug, restores neuroimmune balance. Beyond suppression of inflammasome activation and cytokine production, BRT_002 rescues the integrity

of the DDX5 ribosomal network and normalizes translational homeostasis. Together, these findings define an inflammasome-DDX5-ribosome axis as a fundamental mechanism coupling neuroinflammation to translational failure in the human brain. We established an autologous neurovascular immune brain organoid platform for dissecting human neuroimmune regulation and identifying BRT_002 as a first-in-class modulator of translational homeostasis with therapeutic potential in neurological dysfunction.

Disclosures: N. Metivet: None. **R. Harati:** None. **A. Bouzid:** None. **N. Costa:** None. **C. Disdier:** None. **A. Mabondzo:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.19/Web Only

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

Support: VA merit grant

Title: SIRT3 Activation Enhances the Brain Mitochondrial Function and Microglial Phagocytosis

Authors: *A. TYAGI[1,2], S. RAO[1], J. RAHKOLA[1], J. ARBISER[3], S. PUGAZHENTHI[1]; [1]Rocky Mountain Regional VAMC, Aurora, CO; [2]Univ. of Colorado Sch. of Medicine, Anschutz Med. Campus, Aurora, CO; [3]Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder affecting millions worldwide. It coexists with comorbid conditions such as diabetes, hypertension, and cardiovascular disease, that are collectively associated with metabolic syndrome (MetS). MetS is linked to deficiency of the mitochondrial deacetylase SIRT3. We previously demonstrated that Sirt3 deletion in an AD mouse model exacerbates amyloid plaque accumulation and neuroinflammation. Based on these findings, we hypothesized that SIRT3 represents a promising therapeutic target for AD, particularly in the context of metabolic comorbidities. Honokiol is a natural SIRT3 activator; in this study, we evaluated the efficacy of its analog, honokiol hexafluoro (Hexa), in microglial cells and mouse brain. In BV2 microglial cells, Hexa increased SIRT3 protein levels and reduced lysine acetylation of mitochondrial proteins, a marker of SIRT3 activation. Notably, Hexa treatment significantly decreased BACE1 expression, a key enzyme involved in amyloid-β (Aβ) production from APP. In contrast, co-treatment with the SIRT3 inhibitor 3-TYP reversed these effects, leading to increased mitochondrial protein acetylation and BACE1 expression. BV2 cells treated with Hexa exhibited significantly higher phagocytic activity, an effect that was attenuated by 3-TYP, indicating SIRT3 dependence. In vivo, IP Hexa administration in C57BL/6 mice significantly increased SIRT3 protein levels and reduced mitochondrial protein acetylation and BACE1 expression compared to untreated controls. These effects were absent in Sirt3$^{-/-}$ mice, confirming the specificity of Hexa's action

through SIRT3. Collectively, our findings demonstrate that Hexa exerts beneficial effects via SIRT3 activation, enhancing brain mitochondrial function and promoting Aβ phagocytosis in microglia. These results highlight the therapeutic potential of targeting SIRT3 in neurodegenerative diseases.

Disclosures: A. Tyagi: None. **S. Rao:** None. **J. Rahkola:** None. **J. Arbiser:** None. **S. Pugazhenthi:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.20/X22

Topic: B.09. Glial Mechanisms

Support: NIH R01 HL153176
AHA 24TPA1300008
AHA 25TPA1472723

Title: Therapeutic Potential of Nrf2 Signaling Pathway by Extracellular Vesicles in Neurological Disorders

Authors: E. WANG, X. TIAN, M. ZHENG, E. JI, T. BASNETH, M. ISLAM, L. SUN, *C. TIAN;
Toxicology and Cancer Biol., Univ. of Kentucky, Lexington, KY

Abstract: Therapeutic Potential of Nrf2 Signaling Pathway by Extracellular Vesicles in Neurological DisordersEmma Wang[1,†], Xinyuan Tian[1,†], Maxwell Zheng[1], Edward Ji[1], Tejas Basneth[1], Md Monowarul Islam[1], Lijun Sun[1], Changhai Tian[1,#1]Department of Toxicology and Cancer Biology, University of Kentucky, Lexington, KY 40536. [†]These authors contributed equally to this work; email: tch815@uky.edu

Abstract:

Background: Neurological disorders are leading causes of disability and mortality worldwide, affecting billions of individuals globally. Oxidative stress and neuroinflammation are well-established hallmarks of central nervous system (CNS) disorders. Nuclear factor E2-related factor 2 (Nrf2) is a key transcription factor that coordinates the basal and stress-inducible activation of a vast array of cytoprotective genes, thereby mitigating oxidative stress and attenuating inflammation. While the intracellular functions of Nrf2 signaling in neurological disorders are well documented, how Nrf2 uses extracellular vesicles (EVs) to exert intercellular therapeutic effects remains poorly understood.*Methods and Results:* Using subcellular fractionation alongside *in vitro* EV isolation and characterization, we observed EV-mediated secretion of Nrf2 protein and its downstream targets following the activation of the Nrf2 signaling pathway (Figure 1). Mechanistically, qRT-PCR, western blotting, and co-immunoprecipitation assays revealed that Nrf2 activation upregulates Rab27b, an important

regulator of EV exocytosis, which acts with Nrf2 to facilitate its trafficking and secretion. Furthermore, our preliminary data confirm that Nrf2-enriched EVs exert antioxidant and anti-inflammatory effects in an *in vitro* brain microglial culture. *Conclusions:* Our findings suggest a novel mechanism of EV-mediated Nrf2 secretion that exerts antioxidant and anti-inflammatory effects, offering a promising targeted therapeutic strategy for treating several neurodegenerative diseases.

Keywords: Extracellular vesicles; Nrf2 signaling; Oxidative stress, Neuroinflammation, Neurological disorders

Figure 1

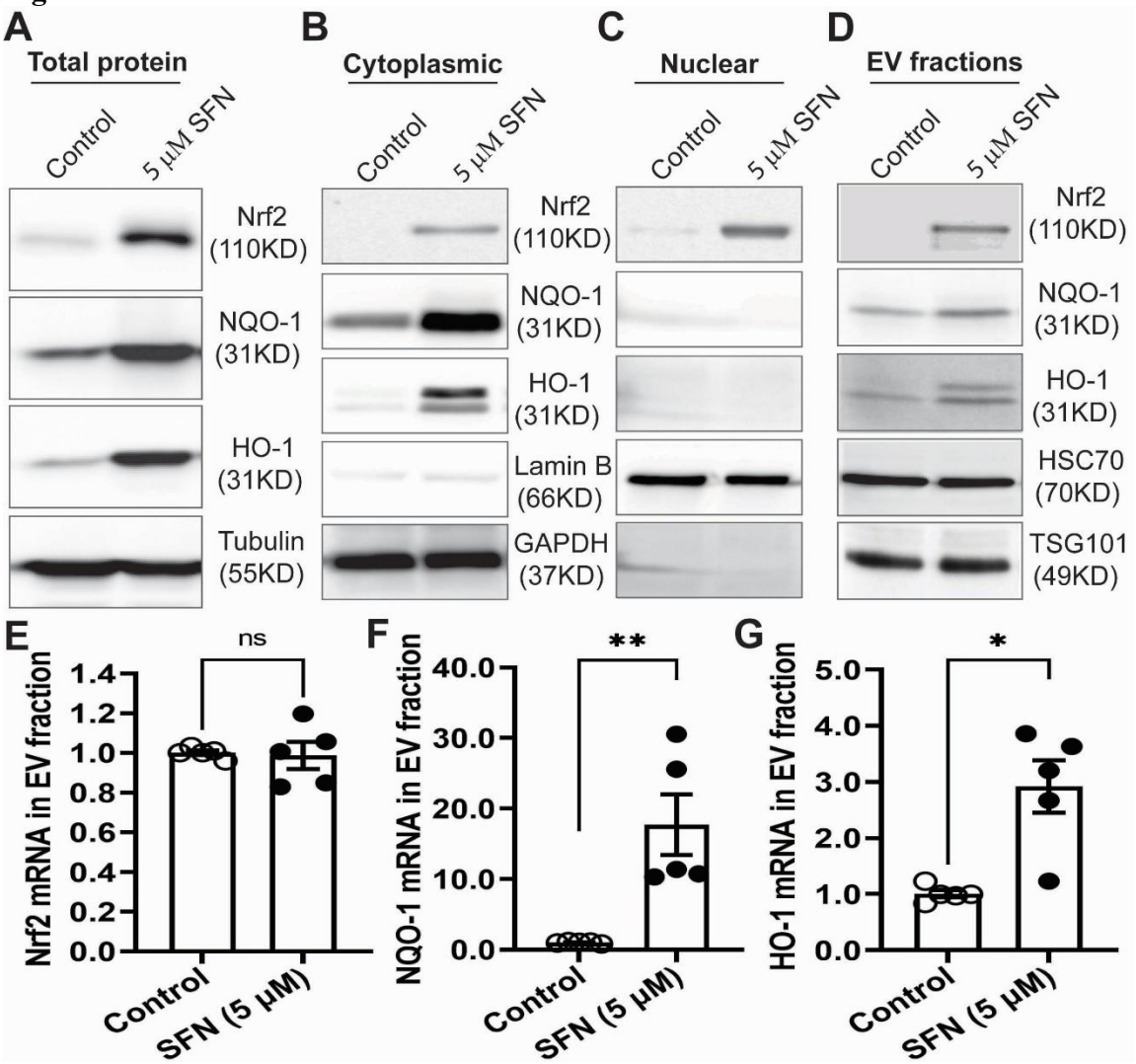


Figure legend: Subcellular distributions and EV enrichment of Nrf2 signaling. Western blot analysis of Nrf2, HO-1, NQO-1, HSC70, TSG101, Lamin B1, and GAPDH across total protein, cytoplasmic, nuclear, and EV fractions. C2C12 cells were treated with vehicle or 5 μM SFN for 24 hours prior to being subjected to nuclear fractionation and EV isolation from conditioned media. (A-D); qRT-PCR: Nrf2 (E), NQO-1 (F), and HO-1 (G) mRNA levels within the EV fractions. GAPDH as an internal control (n=5, ±SEM). *$p < 0.05$; **$p<0.005$.

Disclosures: E. Wang: None. **X. Tian:** None. **M. Zheng:** None. **E. Ji:** None. **T. Basneth:** None. **M. Islam:** None. **L. Sun:** None. **C. Tian:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.21/X23

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

Support: 5R01AG072727-03
SMHS

Title: Decellularization of murine brain tissue for use as a three-dimensional cell culture matrix for studying microglia-amyloid interactions

Authors: *N. FOCSA[1], C. CHENG[3], T. ISHIDA-TAKAKU[4], C. JURGENS[1], C. K. COMBS[2]; [2]Dept of Biomed. Sci., [1]Univ. of North Dakota Sch. of Med., Grand Forks, ND; [3]Univ. of North Dakota, Grand Forks, ND; [4]Biomed. Sci., Univ. of North Dakota Sch. of Med. & Hlth. Sci., Grand Forks, ND

Abstract: The extracellular matrix (ECM) is the natural support structure that surrounds cells in tissues. The ECM regulates how cells grow, move, and interact with their environment. More importantly, cells grown in 3-dimensional cultures within a matrix material can assume a phenotype more representative of the *in vivo* environment compared to those grown in traditional 2-dimensional cultures on tissue culture plastic. For example, microglia have been shown to move throughout the brain, surveilling the local environment and interacting with materials such as fibrillar amyloid deposits. In this study, we worked to standardize a protocol for decellularizing the murine brain to generate an extracellular matrix substrate suitable for studying 3-dimensional microglia-amyloid interactions. As a proof-of-concept, we used the native matrices from 6-month-old C57BL6/J wild-type and App^{NL-G-F} mouse brains to assess their suitability for growth of the murine microglial cell line, SIMA9. The mouse brains were decellularized through a series of detergent and enzymatic treatments. Histologic special stains of the decellularized brains showed effective removal of cellular material, preservation of extracellular matrix collagen and matrix structure, and beta-amyloid-positive plaques in the matrix from App^{NL-G-F} mice. SIMA9 cells were cultured on wild-type and App^{NL-G-F} matrix materials for 4 days, then fixed and imaged via confocal microscopy. CD68-positive SIMA9 staining demonstrated cellular infiltration into the brain matrices as expected. More importantly, SIMA9 cells were able to migrate to and surround beta-amyloid plaques in the App^{NL-G-F} matrix. These data demonstrate that decellularized brain material containing amyloid plaques may serve as a suitable 3-dimensional substrate for studying microglial-amyloid interaction. This model system may prove valuable for future studies of phagocytic clearance, cytokine secretion, phenotypic changes, and migratory behavior when examining microglial interactions with beta-amyloid.

Disclosures: N. Focsa: None. **C. Cheng:** None. **T. Ishida-Takaku:** None. **C. Jurgens:** None. **C.K. Combs:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.22/X24

Topic: B.09. Glial Mechanisms

Title: Development of a proliferative and long-lived hiPSC-derived microglia platform for neuroscience research

Authors: *A. MANTEY, T. TANAKA, L. AGBOR, B. FRAHER, C. TICAS RODAS, C. KETTULA;
Ricoh Biosciences, Inc, Baltimore, MD

Abstract: Microglia are the resident immune cells of the central nervous system and play critical roles in brain development, homeostasis, and neuroinflammatory responses. Human induced pluripotent stem cell (hiPSC)-derived microglia have become valuable tools for studying human neurobiology and neurological disease. However, existing differentiation methods are often limited by finite culture lifespans and restricted proliferative capacity. These limitations can hinder the incorporation of hiPSC-derived microglia into advanced in vitro systems, including central nervous system (CNS) organoid models that require prolonged culture periods.
Using Ricoh Biosciences' proprietary Quick-Tissue™ technology and synthetic mRNA-based programming, we developed an optimized differentiation protocol to generate hiPSC-derived microglia with enhanced proliferative potential and extended culture longevity. Differentiated cells were characterized by Iba1 expression and phagocytic uptake of pHrodo Red E. coli BioParticles. Preliminary studies indicate that almost all of the resulting Iba1-positive cells exhibited phagocytic activity after overnight incubation with the particles, while maintaining sustained expansion and prolonged viability in vitro relative to conventional hiPSC-derived microglia cultures.
The ability to generate proliferative, long-lived microglia may provide a scalable source of human microglial cells for disease modeling, neuroinflammation research, and drug discovery applications. Furthermore, this platform may facilitate the development of more physiologically relevant multicellular CNS models incorporating microglia for the investigation of neurodegenerative and neuroinflammatory disorders. Ongoing studies are focused on further characterization of microglial phenotype and function, as well as evaluation of these cells in complex in vitro model systems.

Disclosures: A. Mantey: None. **T. Tanaka:** None. **L. Agbor:** None. **B. Fraher:** None. **C. Ticas Rodas:** None. **C. Kettula:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.23/X25

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

Support: MSTC 114-2221-E-033 -039 -MY3

Title: Behavioral and Electrophysiological Characterization of Disease Progression in Chemically Induced Rat Models of Alzheimer's Disease

Authors: *S.-C. YU, M.-W. CHAO, C.-Y. TSENG;
Chung Yuan Christian Univ., Taoyuan City, Taiwan

Abstract: Alzheimer’s disease (AD) is characterized by progressive cognitive decline, amyloid-beta accumulation, tau hyperphosphorylation, and neuroinflammation. Because functional impairment emerges after a long preclinical phase, longitudinal animal models that capture early neural dysfunction are needed. In this exploratory study, we characterized behavioral and electroencephalographic changes across disease progression in chemically induced AD-like rat models. Six-week-old Sprague-Dawley rats received D-galactose (D-gal; 100 mg/kg/day), aluminum chloride (AlCl3; 15 mg/kg/day), or D-gal+AlCl3; each group included males and females (3/sex/group; n=6/group). Animals were evaluated at early (week 2), middle (week 4), and late (week 6) stages using the novel object recognition task and Barnes maze. Electroencephalography (EEG) was recorded to quantify spectral power and the theta/alpha ratio. Across induced groups, cognitive performance declined to varying degrees. In the novel object recognition task, only the D-gal+AlCl3 group showed a significant reduction in recognition memory at the middle and late stages. In the Barnes maze, all induced groups showed late-stage impairment in learning-related measures, with the AlCl3 and D-gal+AlCl3 groups displaying the most pronounced memory deficits during the probe test. Sex-stratified analysis revealed that both male and female rats exhibited cognitive decline; however, males showed more consistent changes in escape latency, path length, and probe-test performance, whereas females showed greater inter-individual variability. Based on convergent behavioral measures, the male D-gal+AlCl3 condition provided the most stable AD-like cognitive phenotype. Preliminary EEG analysis showed increased theta/alpha ratio in temporal and parietal regions at the early stage in a subset of induced animals, suggesting early slowing of cortical network activity. Together, these findings identify D-gal+AlCl3 male rats as a stable model for longitudinal AD-like progression and support theta/alpha ratio as a candidate functional marker of early neural-network dysfunction.

Disclosures: S. Yu: None. **M. Chao:** None. **C. Tseng:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.24/X26

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

Support: NIH R01 AG062655
Alzheimer Association SAGA23-1142437

Title: Different effects of sleep deprivation in male and female mice of a novel model of Alzheimer's disease

Authors: *F. DEAK[1,2], A. SETH[1,2], A. M. RAFIQ[1,2], J. B. MILLER[3,2];
[2]Dept. of Neurosci. and Regenerative Med., [1]Augusta Univ., Augusta, GA; [3]Grad. School, Neurosci., Augusta Univ., Augusta GA, GA

Abstract: Objectives: Habitual exposure of acute and chronic stressors were shown to increase the risk of dementia. One of the leading stress factors associated with modern lifestyle is sleep deprivation (SD). To better understand the effects of SD on cognition we designed acute and chronic setting of SD for a novel humanized mouse model of Alzheimer's disease. These mice, called hAbeta KI, express humanized beta-amyloid sequence as part of the original mouse amyloid precursor protein gene. In our studies we used both male and female mice to assess the sex differences as biological variants. We focused on changes in learning and memory and synaptic plasticity.
Methods: We used wild-type and homozygous hAbeta KI mice with normal expression levels of humanized Abeta sequence. We exposed the mice to 48 hours continuous sleep deprivation, once per month, repeated three times. We evaluated the effects of acute and chronic SD on their performance. We compared they behavior in open field, novel object recognition assays before and after SD. We also tested their learning and working memory by analyzing their performance in Y maze test. We measured synaptic plasticity from hippocampal long-term potentiation (LTP) using multi-electrode arrays. We also imaged synaptic neurotransmitter release using FM fluorescence dyes to quantify their vesicular release dynamics.
Results: We detected sex specific differences in the effect of SD on the behavior of hAbeta KI mice. Adult hAbeta KI mice were not cognitively impaired. At one-year of age, the most striking phenotype was their increased deterioration of learning and memory after SD. At 18 mo of age, only female hAbeta KI mice showed almost 50% decrease of LTP in hippocampal CA1 region. We found decreased vesicular release also in cortical neurons of hAbeta KI mice. Interestingly, no senile plaques were present in the brain of hAbeta KI mice.
Conclusions: Acute sleep deprivation had subtle behavioral changes at young adult age of homozygous hAbeta KI mice, while chronic SD altered their hippocampal synaptic function, which led to impaired synaptic plasticity as well as learning and memory under-performance in female hAbeta KI mice. Thus, this novel humanized AD model points to increased sensitivity to SD as probable reason of higher risk of dementia in women and their higher risk of late-onset Alzheimer's disease.

Disclosures: F. Deak: None. **A. Seth:** None. **A.M. Rafiq:** None. **J.B. Miller:** None.

Poster

PSTR223: Neuroinflammation: Novel Models, Methods, and Therapeutics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR223.25/X27

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

Support: LSU Start-Up

Title: Transcriptomic Mapping and Analysis of Region-Specific Microglia States Regulated by Serotonin Stimulation

Authors: S. MOGHIMI, K. REAUX, ***F. KLEMPIN**;
LSU Hlth. New Orleans, New Orleans, LA

Abstract: Emerging evidence suggests that chronic inflammation contributes to neurodegenerative diseases and metabolic disorders. Microglia play a central role in regulating neuroinflammation and neuroplasticity, yet how neuromodulators such as serotonin (5-HT), a target in antidepressant therapy, shape microglia states, phenotypes, and function remains poorly understood. Our previous study showed that microglia express 5-HT receptor subtypes *in vivo*, and that lack of brain serotonin leads to strong upregulation of microglial 5-HT2B and brain-derived neurotrophic factor (BDNF) expression, suggesting adaptation to altered serotonin tone. In parallel, deficiency of the angiotensin-converting enzyme 2 (ACE2), a key regulator of vascular and metabolic homeostasis, reduces serotonin availability and is accompanied by decreased microglial BDNF expression, linking metabolism to serotonin and neuroimmune pathways. Here, we examine transcriptomic responses to physiological (exercise) and pharmacological (SSRI) serotonin stimulation in the hippocampus and hypothalamus, regions involved in distinct cognitive and metabolic functions. We use a targeted spatial transcriptomic panel capturing serotonin signaling, renin-angiotensin system components, neuroplasticity and inflammatory markers, and cell type-specific signatures in neurons and microglia. The transcriptomic profiling identifies stimulus-dependent molecular programs associated with distinct region-specific microglial phenotypes characterized by differential engagement of ACE2 and 5-HT2B-dependent pathways and coordinated microglia-neuron communication. These findings connect serotonin, neuroinflammation, and metabolism and point to microglial pathways as potential therapeutic targets for neuropsychiatric and metabolic disorders.

Disclosures: F. Klempin: None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.01/X28

Topic: D.02. Ischemia

Support: Tata trusts

Title: Transition of endothelial cells triggering blood-brain barrier dysfunction as an indicator to pathological states in neurodegenerative disorders.

Authors: M. PUSHPAM[1], S. SUBRAMANIAN[1], D. ROTTI[2], ***L. DIWAKAR**[1];
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Abstract: Blood Brain Barrier (BBB) plays a very important role to maintain the function of neural networks enabling proper memory function. In mixed dementia conditions caused by metabolic disorders and Alzheimer's disease (AD) BBB breaching is widely reported as an early cause for neurodegeneration. In order to understand the molecular signatures of neurovascular unit, in present study we hypothesize that the endothelial cells (EC) and pericytes transition from a healthy to a pathological state, viz., endothelial-mesenchymal transition in ECs and type 1 to type 2 transitions in pericytes is a key event in BBB breaching. We established streptozotocin (STZ) induced diabetic model in C57BL mice and maintained a state of hyperglycemia (blood glucose >200 mg/dL) for 30 and 60 days. The micro vessels were extracted from the brains to perform immunoblot and immunohistochemical analyses were done from fixed brain sections. The transition markers were also studied from the micro vessels extracted from AD and Control human brain tissues procured from the National Institute for Mental Health and Neurosciences (NIMHANS), Bangalore, India. We found that in diabetic mice (injected with STZ), the mesenchymal markers like vimentin and N-cadherin, and transcription factors like ZEB-1 were upregulated. The upregulation was time-dependent, wherein at the 60-day timepoint exhibited higher expression compared to 30-day indicating the severity of BBB breach in hyperglycemic conditions. We identified a similar expression pattern in micro vessels from the post-mortem human brain tissue. Our data suggest that the BBB undergoes transitions due to pathological conditions and that these transitions happen in a time-dependent manner. This opens avenues for timely therapeutic interventions to prevent the exacerbation of the BBB breach and to potentially develop vascular readouts of neurodegenerative conditions.

Disclosures: M. Pushpam: None. **S. Subramanian:** None. **D. Rotti:** None. **L. Diwakar:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.02/X29

Topic: D.02. Ischemia

Support: PAPIIT IN223226

Title: Overlooked transcription factor: Early B-cell Factor 1 (EBF1) and Blood Brain Barrier

Authors: *J. E. ROGERIO RÍOS, I. PONCE, L. B. TOVAR Y ROMO;
Inst. de Fisiología Celular, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

Abstract: Ischemic stroke is one of the leading causes of death and disability worldwide. After a stroke, the brain vasculature undergoes processes such as angiogenesis before restoring a mature and functional blood-brain barrier (BBB). Vascular endothelial growth factor (VEGF), which is regulated by hypoxia-inducible factor 1 (HIF1), drives this process under hypoxic conditions. We identified Early B-cell Factor 1 (EBF1) as a potential transcription factor regulating VEGF expression, alongside HIF1, under both normoxic and hypoxic conditions. EBF1 expression is enriched in brain vasculature, but it remains unclear whether it is predominantly expressed in endothelial cells or pericytes. While EBF1 is mainly associated with B lymphocytes, its role in the brain and post-stroke recovery processes has been largely overlooked. To explore this, we used primary rat brain microvascular endothelial cells (BMEC) and pericytes and subjected them to oxygen and glucose deprivation (OGD) to assess EBF1-driven expression profiles under normoxic and recovery conditions, as previously identified in a chromatin immunoprecipitation and sequencing (ChIP-seq) assay. We cocultured these cells with primary astrocytes to establish a 2D *in vitro* BBB model to evaluate permeability via transendothelial electrical resistance (TEER) measurements. Finally, we silenced EBF1 expression to determine its relevance in these processes. We found endothelial EBF1 to be downregulated under OGD, followed by 8 h recovery (42% decrease) and 51% decrease upon siRNA-mediated EBF1 knockdown. Furthermore, OGD increased permeability in the BBB model, as determined by TEER. These results suggest that EBF1 may play a role in the recovery and maintenance of BBB function following ischemic injury. Further experiments will help determine how EBF1 regulates these processes. Characterizing the role of EBF1 in angiogenesis and vascular remodeling will contribute to a better understanding of the cellular processes that restore blood flow by promoting blood-brain barrier maturation.

Disclosures: J.E. Rogerio Ríos: None. **I. Ponce:** None. **L.B. Tovar y Romo:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.03/X30

Topic: D.02. Ischemia

Title: Characterizing Acute Neuroinflammation and Microglial Response Following Ischemic Stroke

Authors: *F. PONTARELLI[1], A. CHEONG[2], T. R. HAMMOND[1];
[1]Sanofi, Cambridge, MA; [2]Sanofi-Aventis, Cambridge, MA

Abstract: Ischemic stroke, caused by an acute interruption of cerebral blood flow, triggers extensive neuronal injury and a robust neuroinflammatory response that contributes to secondary brain damage. Innate immune signaling pathways are central to this process, yet the mechanisms regulating the magnitude and persistence of post-ischemic neuroinflammation remain incompletely defined. Various intracellular signaling components involved in inflammatory

pathway activation have been implicated as potential amplifiers of neuroinflammatory responses following ischemic injury. To allow for interrogation of innate immune responses in ischemic stroke, we first wanted to establish a model to characterize the kinetics and magnitude of neuroinflammatory and microglial responses following ischemic stroke.In the first study, we optimized and temporally characterized a transient middle cerebral artery occlusion (MCAO) model in C57BL/6J mice to define the kinetic and spatial dynamics of neuroinflammation and neuronal injury. Brain cytokine profiling revealed an acute pro-inflammatory response within the first hours after MCAO that declined by approximately three days post-injury. Pro-inflammatory cytokine levels were significantly elevated in the ipsilateral hemisphere compared with the contralateral hemisphere, indicating that the inflammatory response originates predominantly from the infarcted tissue. In contrast, plasma neurofilament light chain (NF-L), a marker of axonal injury, increased early after MCAO and remained elevated, consistent with sustained neuronal damage beyond the peak inflammatory phase.Upon validating the model, subsequent studies were used to more fully assess acute peripheral and CNS inflammatory responses and characterize microglial and astrocyte activation. The NULISA mouse120 panel was used to assess plasma and brain 24 hours after reperfusion. Multivariate analyses demonstrated that ischemic injury predominantly drove a brain inflammatory signature with induction of acute inflammatory chemokines, including CXCL1 and CXCL2, as well as increased expression of microglial activation markers such as TREM2, LGALS3, and GPNMB. Immunohistochemical analysis of the brain confirmed the increased microgliosis in ischemic stroke. Together, these findings establish a robust MCAO platform to allow assessment of the contribution of innate immune signaling components to the amplification of acute brain-intrinsic neuroinflammation following ischemic stroke.

Disclosures: F. Pontarelli: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **A. Cheong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi. **T.R. Hammond:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanofi.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.04/X31

Topic: D.02. Ischemia

Support: NIH Grant 1R01NS134993
NIH Grant 3P20GM130447
AHA Postdoc fellowship Grant 25POST1376089

Title: BRD4 inhibition attenuates neuroinflammation and neuronal death in response to global cerebral ischemia

Authors: *H. KIM[1], S. POOJARY[2], P. L. TIWARI[1], R. URQUHART[1], A. DASH[2], J.-Y. HWANG[1];
[1]Pharmacol. and Neurosci., Creighton Univ. Sch. of Med., Omaha, NE; [2]Pharm., Creighton Univ. Sch. of Pharm. and Hlth. Professions, Omaha, NE

Abstract: Global cerebral ischemia most commonly caused by cardiac arrest, leading selective and delayed death of hippocampal CA1 pyramidal neurons, subsequently inducing the severe cognitive deficits. Although this phenomenon is well-known, the underlying molecular mechanisms of neuronal death and the associated cognitive deficits remain unclear. To identify key regulators involved in global ischemia-induced neuronal death, we performed RNA-seq of the hippocampal CA1 at 24h and 48h after global ischemia. Ingenuity Pathway Analysis (IPA) of differentially expressed genes (DEGs) identified inflammatory-related pathways, including TREM1 signaling, among the top canonical pathways. In addition, a set of genes, including BRD4, was identified as the predicted transcriptional upstream regulators of these canonical pathways. BRD4, an epigenetic reader that recognizes acetylated lysine residues, plays a critical role in the transcriptional regulation of inflammatory genes and has been previously reported to regulate TREM1 expression. Therefore, we hypothesized that global ischemia activates BRD4 and neuroinflammation through the epigenetic regulation of TREM1. We first confirmed that BRD4 expression was increased at 24h and 48 h after global ischemia, and TREM1 mRNA and protein levels were also increased at these time points. Consistent with these findings, pro-inflammatory cytokines were significantly increased in the hippocampal CA1 at 48 h. Using immunohistochemistry, we found that BRD4 co-localized with TREM1-positive cells. Furthermore, ChIP assay revealed that BRD4 binds to the TREM1 promoter following oxygen-glucose deprivation *in vitro*. Importantly, BRD4 inhibition by siBRD4-loaded nanoparticles attenuated microglia activation, and ultimately prevented neuronal death in the hippocampal CA1 after global ischemia. Taken together, these findings suggest that BRD4 upregulates TREM1 expression, which in turn enhances neuroinflammation and promotes neuronal death in the hippocampal CA1 after global ischemia, implicating BRD4 as a potential therapeutic target.

Disclosures: H. Kim: None. **S. Poojary:** None. **P.L. Tiwari:** None. **R. Urquhart:** None. **A. Dash:** None. **J. Hwang:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.05/X32

Topic: D.02. Ischemia

Support: AHA Grant 26PRE1559777
NIH/NINDS Grant R37NS067525

Title: A novel parthanatos inhibitor reveals a PAR-dependent chromatin remodeling mechanism in ischemia-induced cell death

Authors: *L. C. GUTTMAN[1], B. KANG[2], S.-Y. KIM[2], J. PARK[2], C.-H. NA[2], V. L. DAWSON[3], T. M. DAWSON[3];
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Abstract: Ischemic stroke is a leading cause of neurological disability and death, yet treatment options remain suboptimal. Parthanatos is a major regulated cell death pathway implicated in ischemia-induced neuronal loss and its molecular mediators are promising therapeutic targets. Following excessive DNA damage, PARP-1 becomes activated and produces pathological poly(ADP-ribose) (PAR) polymers that translocate to the cytosol and promote AIF release from the mitochondria. AIF then forms a complex with MIF and co-translocates to the nucleus, where MIF, a member of the PD-D/E(X)K nuclease family, fragments DNA and drives cell death. A MIF nuclease inhibitor, termed PAANIB-1, prevents parthanatos and confers neuroprotection in Parkinson's disease and stroke models. MIF nuclease inhibitor compound screening unexpectedly identified a novel parthanatos inhibitor (C8-33) that prevents PARP-1 dependent cell death while preserving MIF nuclease activity, suggesting a distinct mechanism. Here, we used C8-33 as a chemical tool to identify a previously unrecognized chromatin remodeling mechanism in parthanatos. Thermal proteome profiling-temperature range (TPP-TR) identified C8-33-binding proteins, and a follow-up siRNA screen nominated a protein, designated PACR-1 (Parthanatos-Associated Chromatin Remodeler-1), as the top functional candidate. C8-33 potently protected SH-SY5Y cells from N-methyl-N′-nitro-N-nitrosoguanidine (MNNG)-induced cell death and primary cortical neurons in ischemia-relevant injury models. Genetic loss of PACR-1 was similarly neuroprotective and occluded the protective effects of C8-33. Mechanistically, C8-33 suppressed γH2AX signaling and DNA fragmentation, and these effects were lost in PACR-1 depleted cells. Chromatin fractionation revealed that PACR-1 becomes further engaged with chromatin during parthanatos, supporting a model in which PACR-1 promotes DNA damage signaling. PACR-1 bound PAR through a charge-dependent interface, and disruption of this PAR-binding region decreased γH2AX signaling and altered PAR responses. ATAC sequencing revealed that ~70% of C8-33-induced chromatin remodeling under MNNG treatment was dependent on PACR-1, providing genome-wide evidence that C8-33 acts through PACR-1. Together, these findings identify PACR-1 as a novel therapeutic protein target that couples PAR signaling to chromatin remodeling, DNA damage amplification, and neuronal death during parthanatos. This work establishes C8-33 as a potent parthanatos inhibitor and a promising, disease-modifying, drug candidate for stroke therapy.

Disclosures: L.C. Guttman: None. **B. Kang:** None. **S. Kim:** None. **J. Park:** None. **C. Na:** None. **V.L. Dawson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins University. **T.M. Dawson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins University.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.06/Y1

Topic: D.02. Ischemia

Support: DGAPA-PAPIIT IN214723

Title: Genetic suppression of ASK1 in human neurons as an in vitro proxy of ischemic neuronal death

Authors: *N. ACEVEDO[1], R. A. SANTANA[2], I. VELASCO[3], L. B. TOVAR Y ROMO[2];
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Abstract: Apoptosis signal-regulating kinase 1 (ASK1), a pivotal mitogen-activated protein kinase kinase kinase (MAP3K), regulates cell fate through extensive protein-protein interactions (PPIs). During ischemic stroke, ASK1 activation primarily initiates apoptosis via the p38 and JNK MAPK pathways, compromising neuronal survival. However, ASK1 also participates in survival pathways, though these dual molecular mechanisms remain poorly understood. Here, we investigated whether ASK1 functions as a molecular switch during the neuronal response to ischemic stroke. Using CRISPR/Cas9 ribonucleoprotein (RNP) complexes, we generated an ASK1-knockout (ASK1ko) human embryonic stem cell (hESC) line. Despite requiring multiple attempts to obtain a homozygous clone, the engineered line maintained pluripotency with no detectable off-target effects. We then differentiated these ASK1ko hESCs into dopaminergic neurons using a floor-plate protocol. The ASK1ko neurons showed no phenotypic deviations from controls but exhibited significantly enhanced viability. To dissect the regulatory PPIs driving this phenotype, we engineered specific point mutations within key residues of the ASK1 interaction sites. Ongoing experiments introducing these mutants into ASK1ko neurons will elucidate ASK1's functional dynamics post-ischemia, providing new insights into its dualistic role in neuronal fate determination.

Disclosures: N. Acevedo: None. **I. Velasco:** None. **L.B. Tovar y Romo:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.07/Y2

Topic: D.02. Ischemia

Title: Spatial heterogeneity of cellular responses in the post-stroke brain

Authors: *B. DEREBERY[1], M. KENWOOD[2], D. BETZ[3], E. GUTIERREZ KURI[4], J. P. PALAVICINI[5], M. P. GOLDBERG[6];
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Abstract: Stroke triggers a region-specific cellular response that is heavily reliant on the neuronal circuitry of the injury site. Rodent model work has demonstrated that proximal and remote areas that receive connections from and to the injury site can be subjected to multimodal inflammatory responses. Single-cell sequencing studies have focused on these cell type responses within the ischemic region but lack neurons and crucial spatial context of lesion proximity, connectomics, and cellular neighborhoods. To address this gap we used spatial transcriptomic RNA sequencing to investigate connectomic guided responses to cortical ischemic injury at 7-days post-stroke, a critical time for neuroplasticity. Leveraging a purpose built single-cell & single-nucleus atlas we achieve high specificity of cell type annotation decoding spatially segregated cell types. Astrocytes and myeloid cells were enriched in areas that directly projected to the ischemic region in the homotopic contralesional cortex (CLC). Neurons surrounded by these proinflammatory glial cells had a higher growth associated gene expression response. Taken together, these data highlight the spatial heterogeneity of immune cell responses to localized damage and implicate neuronal connectivity based glial activation as a driver of neuronal plasticity.

Disclosures: B. Derebery: None. **M. Kenwood:** None. **D. Betz:** None. **E. Gutierrez Kuri:** None. **J.P. Palavicini:** None. **M.P. Goldberg:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.08/Y3

Topic: D.02. Ischemia

Title: Mapping proteomic signatures to transcriptional states in human ischemic stroke using sequential spatial multiomics

Authors: *K. YOUNG[1], **K. CHAVDA**[2], A. LASLEY[1], G. ONG[3], B. FILANOSKI[1], L. HAMANISHI[1], A. L. HECK[1], M. HOANG[1], J. BEECHEM[4], E. HOBBS[5];
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Abstract: Ischemic stroke induces spatially complex microenvironments shaped by the interactions between resident glial populations, infiltrating immune cells, and the injured vasculature. Defining the molecular architecture of these environments remains a major challenge, as conventional approaches like bulk and single-cell molecular profiling methods

typically lose the spatial context necessary for understanding the post-stroke environment.Here, we apply a sequential spatial multiomics workflow to the same formalin-fixed paraffin-embedded (FFPE) human ischemic stroke tissue to map proteomic niches and their underlying transcriptional states across infarct and peri-infarct regions. Using the GeoMx® Digital Spatial Profiler (DSP) with the Discovery Proteome Atlas (DPA), an antibody panel comprising >1,200 protein targets, we profiled regions of tissue damage and immune activity in the post-stroke brain. The breadth of this panel enables rich characterization of diverse signaling pathways, extending beyond canonical markers to capture complex processes underlying neuroinflammation, vascular remodeling, and tissue repair.Spatial proteomics revealed distinct region-specific molecular profiles. Infarct cores were characterized by signatures associated with significant immune activation, proteolysis, and vascular disruption, while peri-infarct regions showed patterns consistent with reactive gliosis and tissue reorganization. Notably, heterogeneous proteomic niches emerged within these regions, suggesting localized microenvironments that may differentially support immune cell recruitment and functional specialization.To resolve the cellular basis of these niches, the same tissue sections were subsequently analyzed using the CosMx® Spatial Molecular Imager (SMI) Whole Transcriptome Panel (WTX), covering >18,000 protein-coding genes, enabling single-cell spatial mapping of transcriptional states. This approach directly links region-level protein signatures to the cellular composition and gene expression patterns present within each region, revealing distinct cell types and states associated with specific proteomic environments.Together, this study shows how combining ultra-high-plex spatial proteomics with single-cell transcriptomics on the same tissue section links the broader tissue microenvironment with specific cell-level gene expression. By defining how proteomic signatures map to underlying transcriptional states, this framework provides a comprehensive approach for dissecting the spatial organization of neuroinflammation and immune remodeling in ischemic stroke.

Disclosures: K. Young: A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **K. Chavda:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **A. Lasley:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **G. Ong:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **B. Filanoski:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **L. Hamanishi:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **A.L. Heck:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **M. Hoang:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **J. Beechem:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA. **E. Hobbs:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology, Seattle, WA, USA.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.09/Y4

Topic: D.02. Ischemia

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

Title: A single-cell transcriptomic atlas of the rodent renovascular hypertension model implicates interferon-mediated intercellular signaling between oligodendrocyte and macrophage in ischemic white matter injury

Authors: *S. SINGH[1], H. SEO[3], X. JIN[5], H. KIM[6], E. LEE[2], B. G. KIM[7,4];
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Abstract: White matter hyperintensities (WMH) reflect cerebrovascular pathology characterized by demyelination and axonal degeneration in the white matter. Our previous study showed that renovascular hypertension in rats produces pronounced degeneration in the corpus callosum, accompanied by WMH on MRI. In this study, a two-kidney, two-clip renovascular hypertensive rat model was stratified based on MRI findings into sham, WMH-negative, and WMH-positive groups. Single-cell RNA sequencing of the corpus callosum characterized the transcriptional profiles of macrophages and oligodendrocytes (OLs). OLs were classified into four subclusters: interferon-associated OLs (IFOL), stress-induced OLs (SIOL), mature OLs, and proliferating OLs. Both IFOL and SIOL were enriched only in WMH-positive rats. IFOLs were marked by IFI27 (Interferon Alpha Inducible Protein 27) and IRF7 (Interferon Regulatory Factor 7) and characterized by signaling pathways related to interferon production. Expansion of proliferating OLs marked by BMP-4 (Bone Morphogenetic Protein 4) in WMH-negative rats suggests that these OLs may represent a stress-resilient population. A trajectory analysis suggested that ischemic stress induces proliferating OLs, which sequentially transition into SIOLs and IFOLs as WMH pathology manifests. Macrophages formed five subclusters: homeostatic, border-associated macrophage, focal white matter injury, axon tract-associated, and proliferating. All clusters except the homeostatic cluster were enriched in the WMH-positive group, including pathways related to interferon signalling, oxidative stress, and chemokine signalling. CCL7 was markedly enriched in the focal white matter injury subcluster, as confirmed by immunohistochemistry, which showed its colocalization with CD11b-positive cells adjacent to degenerating axons. Recombinant CCL7 treatment of mature oligodendrocytes induced dose-dependent cytotoxicity and myelin loss, as demonstrated by LDH assays and reduced MBP immunoreactivity. These findings led us to hypothesize that the shift of OLs from a proliferating, resilient population to IFOLs may represent a pivotal step in exacerbating CCL7+ macrophage-induced white matter injury in this model. We are currently investigating OL-macrophage crosstalk mediated by interferon signaling using the microglia-OL co-culture paradigm.

Disclosures: S. Singh: None. **H. Seo:** None. **X. Jin:** None. **H. Kim:** None. **E. Lee:** None. **B.G. Kim:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.10/Y5

Topic: D.02. Ischemia

Support: AHA Grant 24CDA1269588

Title: Wavelength-dependent photobiomodulation regulates oligodendroglial-to-endothelial paracrine signaling after oxygen-glucose deprivation

Authors: *J. ZHANG[1], N. YANG[2], Q.-G. ZHANG[3], X. ZONG[3];
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Abstract: Chronic cerebral hypoperfusion (CCH) damages cerebral white matter through coupled injury to oligodendrocyte-lineage cells and the microvasculature. Reciprocal signaling between oligodendrocyte precursor cells (OPCs) and endothelial cells is essential for white matter repair, but whether photobiomodulation (PBM) restores this crosstalk remains unknown. We hypothesized that PBM promotes oligodendroglial-to-endothelial paracrine signaling in a wavelength-dependent manner following ischemic injury.
Oli-neu cells (OPC-like; dibutyryl-cAMP-induced differentiation) and bEnd.3 brain endothelial cells underwent oxygen-glucose deprivation/reoxygenation (OGD/R). PBM was delivered at 810 and 1064 nm (50 mW/cm², 15 J/cm²). Directional crosstalk was evaluated using conditioned-medium transfer and transwell co-culture. Oligodendroglial viability and differentiation, endothelial barrier integrity, angiogenic activity, and tight-junction protein expression were assessed. Bulk transcriptomic and proteomic profiling of PBM-treated Oli-neu cells was integrated with our in vivo hippocampal datasets using RRHO2, pre-ranked GSEA, and ligand-receptor analysis to identify candidate mediators of oligodendroglial-to-endothelial communication.
Compared with 1064-nm PBM, 810-nm PBM increased oligodendroglial viability, MBP/OLIG2 expression, and cytochrome-c oxidase activity following OGD/R. Conditioned medium from PBM-treated oligodendroglial cells enhanced endothelial barrier integrity, as evidenced by increased TEER and Claudin-5 expression and reduced FITC-dextran permeability, whereas conditioned medium from OGD-only cells produced no protective effects. Integrated transcriptomic, proteomic, and ligand-receptor analyses identified candidate mediators of oligodendroglial-to-endothelial communication, providing a foundation for future mechanistic studies. Together, these findings identify a wavelength-dependent oligodendroglial-to-endothelial paracrine mechanism underlying PBM-mediated white matter protection after CCH and link our in vitro findings with in vivo observations.

Disclosures: J. zhang: None. **N. Yang:** None. **Q. Zhang:** None. **X. zong:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.11/Y6

Topic: D.02. Ischemia

Support: NIH NINDS Grant R01NS122961
Mission Connect, a program of TIRR Foundation, Grant 019-117
Mission Connect, a program of TIRR Foundation, Grant 021-103

Title: Whole-Spinal Cord Imaging Platform to Characterize Ischemia and Vascular Remodeling Following Spinal Cord Injury

Authors: *A. BUXTON[1,2], L. VILLANUEVA[3], H. SINGH[2], M. HRUSKA[3,4], D. A. MCCREEDY[3,2,5];
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Abstract: Spinal cord injury (SCI) is a debilitating condition that affects around 300,000 people in the United States. The initial mechanical trauma to the spinal cord damages local vasculature and disrupts the blood-spinal cord barrier, exacerbating inflammation and tissue degeneration. Although endogenous revascularization occurs after injury, the newly formed vessels are often structurally and functionally inadequate. Current strategies for measuring revascularization after SCI overwhelmingly rely on assessing vessel density and perfusion near the lesion epicenter, providing only a partial view of vascular remodeling. However, these conventional metrics fail to capture critical morphological changes that may underlie impaired function and secondary injury, while also neglecting potential changes in distal spinal cord regions. As a result, our understanding of spinal cord vascular remodeling is fundamentally limited, potentially obscuring key mechanisms that could inform more effective therapies. To address these limitations, we have optimized tissue clearing and vasculature labeling techniques to quantify both local and distal spinal cord vascular remodeling following SCI. To visualize post-injury vasculature, mice were perfused with wheat germ agglutinin (WGA)-488, a fluorescently tagged lectin that binds glycoproteins on vascular endothelial cells. The vasculature was then cast with gelatin containing Evans Blue dye complexed with bovine serum albumin (EB-BSA), which together fluoresce at 647 nm. Combined with tissue clearing and light-sheet microscopy, this dual-labeling approach yields high-resolution, three-dimensional visualization of perfused vasculature throughout the entire spinal cord. Qualitative results indicate that a lower thoracic (T9) contusion injury induces extensive ischemia that propagates throughout the thoracic spinal cord, persisting for up to 3 days. This profound and prolonged hypoperfusion likely contributes to secondary injury and could create a significant barrier to endogenous repair. By 7 days post-injury, newly formed vessels are notably thicker and exhibit reduced density in the lesion epicenter, suggesting an altered and potentially maladaptive pattern of vascular regeneration. In addition to these qualitative observations, additional quantitative analyses will assess temporal and spatial changes

in vessel density, branching density, vessel length, and vessel diameter along the spinal cord. The imaging and analytical methods established in this study can be employed to evaluate how therapeutic interventions impact vascular remodeling and recovery following spinal cord injury.

Disclosures: A. Buxton: None. **L. Villanueva:** None. **H. Singh:** None. **M. Hruska:** None. **D.A. McCreedy:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.12/Y7

Topic: D.02. Ischemia

Support: AHA Postdoctoral Fellowship. 26POST1549522
NIH Grant R01. 1R01NS144556-01A1
The Jacskson Laboratory Institutional Startup funds

Title: Projection-selective IT circuit plasticity in secondary motor cortex during dexterous recovery after stroke

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Abstract: After primary motor cortex (MOp) stroke, dexterous function partially recovers despite persistent kinematic deficits. The circuit mechanisms supporting recovery after loss of primary motor output remain undefined. Plasticity in secondary motor cortex (MOs) correlates with recovery across species, yet the excitatory pyramidal cell types driving endogenous recovery are unresolved. Within MOs, intratelencephalic (IT) neurons encode motor commands for dexterous function upstream of descending output. IT neurons provide inputs to contralateral striatum (cs-IT) or contralateral cortex (cc-IT), suggesting distinct subtypes play different roles in circuit remodeling after stroke. We tested whether post-stroke plasticity is projection-selective within IT. Adult C57BL/6J mice of both sexes (n=3-8 per group) were trained on a freely-moving dexterous reaching task measuring unimanual and bimanual dexterity. High-speed video (500fps) and deep learning models (DeepLabCut, DeepEthogram) extracted kinematic and ethological features. Following photothrombotic stroke to MOp, behavioral analysis revealed peak kinematic impairment at day 7 and a recovery plateau at day 21. These timepoints, within the known critical window of post-stroke plasticity, guided closed-loop optogenetic silencing (stGtACR2) of pan-excitatory and IT sub-class populations during specific reaching phases. MOp stroke caused persistent deficits in reaching kinematics and dexterous movements. In healthy animals, pan-excitatory silencing of MOp or MOs blocked reach progression, consistent with prior studies. Similar effects were observed when selectively silencing either cc-IT or cs-IT in MOs, extending these findings to projection-defined IT classes. After stroke, perturbations of IT sub-classes produced more profound and distinct effects: silencing evoked bilateral

coordination deficits ($p<0.01$) and postural destabilization ($p<0.001$) not observed pre-stroke, with longer recovery times to reinitiate movement. Together, our results demonstrate the causal and continued role of MOs IT neurons in skilled motor function after stroke. Projection-defined IT subclasses are not redundant but make distinct contributions to circuit remodeling. The exacerbation of silencing phenotypes suggests recovery depends on altered weighting of surviving MOs circuits, in which IT activity becomes increasingly important for supporting restored dexterous movements. Ongoing projection-resolved neural activity recordings are addressing the synaptic basis of these changes.

Disclosures: M. Alasoadura: None. **M. Joy:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.13/Y8

Topic: D.02. Ischemia

Support: NIH R01 NS119166

Title: High-fat diet exacerbates neuroinflammation and cognitive impairment in mouse model of VCID

Authors: *M. RAHMAN[1,2,3], M. SULTAN[3], K. HABIB[3], S. KUNDU[2,3], B. SARKER[2,3], I. JAHAN[3], M. BHUIYAN[3,2,4];
[2]Pathology and Translational Pathobiology, [3]Neurol., [4]Inst. for Cerebrovascular and Neuroregeneration Res. (ICNR), [1]LSU Hlth. Shreveport, Shreveport, LA

Abstract: Background:Obesity affects >100 million U.S. adults and increases the risk of late-life dementia by ~30%. Obesity promotes blood-brain barrier dysfunction and chronic cerebral hypoperfusion, key features of vascular contributions to cognitive impairment and dementia (VCID). However, the mechanisms linking obesity to VCID remain poorly understood. High-fat diet (HFD)-induced obesity elevates circulating lipids and disrupts metabolic homeostasis. Emerging evidence suggests that reactive astrocytes produce toxic lipids that contribute to oligodendrocyte and neuronal injury. Whether HFD promotes brain toxic lipid accumulation and exacerbates VCID pathology remains unknown. Here, we investigated whether HFD worsens bilateral carotid artery stenosis (BCAS)-induced VCID-like pathology. **Methods**: Five-week-old male C57BL/6J mice were fed a 45% or 60% HFD for 6 weeks before sham or BCAS surgery. Cerebral blood flow (CBF) was measured by laser speckle imaging, and cognitive function was assessed using the Morris water maze 6 weeks after BCAS. Astrogliosis was evaluated by immunofluorescence and immunoblotting, and cell type-specific transcriptional profiles of ACSA-2^+ astrocytes were analyzed by RNA-sequencing. **Results**: HFD reduced CBF independent of BCAS and caused progressive mild cognitive impairment, while combined with BCAS induced severe cognitive deficits compared to sham and BCAS control. Behavioral

changes were accompanied by reduced myelin basic protein (MBP), indicating axonal demyelination. Notably, 60% HFD induced severe cognitive impairment even in the absence of BCAS. HFD significantly increased GFAP^{+} reactive astrocytes and Iba1+ microglia/macrophages. RNA-sequencing of ACSA-2^{+} astrocytes revealed enrichment of fatty-acid elongation, sphingolipid metabolism, and inflammatory pathways. HFD increased expression of astrocytic lipid synthesis genes (Elovl1, Elovl7, Cers2, and Cers6) and inflammatory genes (Lcn2, Mmp9, Cxcl2, Il1b, Il33, and Itgam), whereas HFD+BCAS further elevated Casp1, Mmp9, Ccl2, Ccr5, and Cx3cr1. Analysis of published single-nucleus RNA-sequencing datasets corroborated our findings, demonstrating increased expression of astrocytic lipid synthesis gene expression in obese mice.**Conclusion**: HFD-induced obesity promotes reactive astrogliosis, toxic lipid synthesis, white matter injury, and cognitive impairment, and exacerbates chronic cerebral hypoperfusion-induced VCID pathology. Astrocytic lipid signaling may represent a potential therapeutic target for obesity-associated VCID.

Disclosures: M. Rahman: None. **M. Sultan:** None. **K. Habib:** None. **S. Kundu:** None. **B. Sarker:** None. **I. Jahan:** None. **M. Bhuiyan:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.14/Web Only

Topic: D.02. Ischemia

Title: Expression of PHB-1 and PHB-2 in human brain tissue after cerebrovascular event

Authors: F. URIARTE JIMÉNEZ[1], J. PEÑALOZA ALBARRAN[1], A. SÁNCHEZ GARCÍA[1], F. CÁZARES-RAGA[2], J. NADER[4], F. HERNÁNDEZ HERNÁNDEZ[3], ***A. ORTIZ-PLATA**[5]; [1]Neuropatología Exptl., Inst. Nacional de Neurología y Neurocirugía, México, Mexico; [2]Infectómica y Patogénesis Mol., CINVESTAV-IPN, Ciudad de Mexico, Mexico; [3]Infectómica y Patogénesis Mol., CINVESTAV-IPN, México, Mexico; [4]Medica Sur, México, Mexico; [5]Natl. Inst. of Neurol. and Neurosurg., México, Mexico

Abstract: Brain ischemia is a leading cause of disability and mortality worldwide. In cerebral ischemia,there is an interruption of blood flow causing genetic and proteomic alterations. In previousproteomic study of focal cerebral ischemia in rats Prohibitin-1 was identified as a differentialprotein; however, its expression has not been analyzed in post-stroke human brain tissue.Prohibitins (PHBs) are pleiotropic proteins commonly located in the mitochondrial inner middlelayer (IML); they comprise two types: PHB1 and PHB2. We analyzed PHB expression in humanbrain tissue in autopsies diagnosed with a cerebrovascular event. From the Department ofNeuropathology-INNN (project 181-22), seven autopsy cases diagnosed with stroke werestudied. Immunohistochemistry for PHB-1 and PHB-2 proteins was performed on 5 µm sections,and the ischemic cortex was analyzed using conventional light microscopy. All cases showedcytoplasmic positivity for PHB-1, of which 85% (n=6) showed positivity for PHB-2 in

the sameareas, which agrees with the mitochondrial localization described for these proteins,predominant in regions with hypoxic-ischemic changes. PHB play a key role in genomemaintenance and stability, regulation of the oxidative phosphorylation pathway, andpreservation of mitochondrial function and stability. Under stress, they exhibit protectiveproperties against excitotoxicity, reactive oxygen species (ROS), and apoptosis inducers. In ratmodels of focal cerebral ischemia, PHB overexpression acts as a cellular protector, reducing ROSproduction, preserving the integrity of the outer mitochondrial membrane, and preventing theactivation of apoptotic pathways. Conversely, its suppression has been observed to make neuronsmore vulnerable to hypoxic injury and increase ROS production. This study demonstrates, for thefirst time, the expression of PHB-1 and PHB-2 in human brain tissue obtained from autopsies ofpatients diagnosed with ischemic stroke. Both proteins showed predominant immunoreactivityin regions with hypoxic-ischemic cellular changes, consistent with findings described in animalmodels, which may have implications for their neuroprotective potential.

Disclosures: F. Uriarte Jiménez: None. **J. Peñaloza Albarran:** None. **A. Sánchez García:** None. **F. Cázares-Raga:** None. **J. Nader:** None. **F. Hernández Hernández:** None. **A. Ortiz-Plata:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.15/Y9

Topic: A.01. Neurogenesis and Gliogenesis

Support: Roy J Carver Chair of Molecular Medicine, to John Engelhardt

Title: Nox2 Inhibition Promotes Neurogenesis and Motor Recovery After Stroke

Authors: *W. S. A. SHAHIN[1], S. EBED[2], K. PAREKH[1], J. F. ENGELHARDT[3]; [1]Cardiothoracic Surgery, The Univ. of Iowa, Carver Col. of Med., Iowa City, IA; [2]Family Med., Indian Regional Med. Ctr., Indiana, PA; [3]Dept. of Med., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Background: Stroke remains a leading cause of disability and death with limited therapeutic options. While oxidative stress is stroke-associated and generally pathological, reactive oxygen species (ROS) paradoxically regulate adult neurogenesis. The relationship between ROS-mediated neurogenesis and poststroke recovery remains poorly understood. We hypothesized that modulating ROS through NADPH oxidase 2 (Nox2) inhibition would enhance post-stroke neurogenesis and promote functional recovery. **Methods:** 10-week-old male mice underwent 30-minute transient middle cerebral artery occlusion (tMCAO). Beginning 5 minutes before reperfusion, mice received intraperitoneal apocynin (Nox2 inhibitor) or vehicle for 5 consecutive days. Cerebral infarction volume was quantified by MRI at 48 hours. Motor

recovery was assessed via gait analysis at baseline, 10, and 30 days post-stroke. Neurogenesis was evaluated by immunofluorescence labeling and quantification in multiple CNS regions. Given that apocynin inhibits Nox2 by preventing recruitment of Ncf1, findings were validated in *Ncf1*$^{-/-}$ mice. **Results:** Nox2 inhibition significantly promoted expansion of neural progenitors (Nestin^{+} BrdU^{+} and Dcx^{+} BrdU^{+} cells) and A2 reactive astrocytes (S100A10^{+} cells) in the infarction 6 days after tMCAO. Additionally, Nox2 inhibition enhanced neuroprotection and neurogenesis in the striatum as indicated by the significantly higher percentage of NeuN^{+} and NeuN^{+} BrdU^{+} cells respectively in the infarcted striatum of apocynin-treated mice 30 days after stroke. This increase in neurogenesis correlated with significantly improved motor recovery through day 30 post-stroke as indicated by increased stride length, and prolonged stance and brake durations of the apocynin-treated mice compared to vehicle-treated counterparts. Outcomes using *Ncf1*$^{-/-}$ mice were similar to apocynin treatment, validating Nox2 as a critical regulator. **Conclusions:** These findings establish Nox2 as a negative regulator of post-stroke neurogenesis and identify a paradoxical role for ROS in stroke recovery. Nox2 inhibition promotes neurogenesis and translates to improved functional outcomes, suggesting therapeutic potential for stroke patients.

Disclosures: W.S.A. Shahin: None. **S. Ebed:** None. **K. Parekh:** None. **J.F. Engelhardt:** None.

Poster

PSTR224: Stroke, Ischemia, and Vascular Injury: Mechanistic Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR224.16/Y10

Topic: D.02. Ischemia

Support: NIH Grant R01 NS119166

Title: Role of IL-18/MyD88 Signaling in Neuroinflammation and Cognitive Impairment in VCID

Authors: *M. SULTAN[1], M. HABIB[2], M. RAHMAN[2,3], S. KUNDU[2,3], B. SARKER[2,3], I. JAHAN[2], M. BHUIYAN[2,3,4];
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Abstract: Background: Vascular contributions to cognitive impairment and dementia (VCID) are a major cause of dementia and are characterized by reactive astrogliosis, microglial activation, blood-brain barrier disruption, white matter injury, and cognitive decline. However, the molecular mechanisms driving VCID remain poorly understood. Elevated levels of the proinflammatory cytokine interleukin-18 (IL-18) have been reported in plasma, cerebrospinal fluid, and brain tissue of VCID patients, suggesting a potential role in disease pathogenesis. Here, we investigated whether IL-18 deficiency attenuates chronic cerebral hypoperfusion-

induced VCID pathology and whether pharmacological inhibition of MyD88, a key downstream mediator of IL-18 signaling, mitigates neuroinflammation and cognitive impairment. **Methods**: Chronic cerebral hypoperfusion was induced by bilateral carotid artery stenosis (BCAS) using 0.18-mm microcoils placed around both common carotid arteries in wild-type (WT) and global IL-18 knockout (IL-18 KO) mice. To assess therapeutic potential, WT mice received TJ-5 (10 mg/kg, i.p.), a selective MyD88 inhibitor, from 2-6 weeks after BCAS. Cerebral blood flow (CBF) was measured by laser speckle imaging, and cognitive function was evaluated using the Morris water maze. Expressions of IL-18, IL-18R1, MyD88, NF-κB, C3d, LCN2, and myelin basic protein (MBP), astrogliosis, and microglial activation were assessed by immunofluorescence staining. **Results:** WT mice exhibited chronic CBF reduction, white matter demyelination, as indicated by decreased MBP, hippocampal neuronal loss, and cognitive deficits 8 weeks after BCAS. IL-18 and IL-18R1 expression in the corpus callosum (CC) increased from the early (1 week) to late (8 weeks) stages following BCAS. WT mice also showed marked increases in $GFAP^{+}C3d^{+}$ cytotoxic astrocytes, LCN2, MyD88 expression, and NF-κB phosphorylation and nuclear translocation. In contrast, IL-18 deficiency attenuated these inflammatory responses, preserved MBP levels, and improved spatial learning and memory, indicating that IL-18 promotes VCID pathology by activating the MyD88-NF-κB signaling pathway. Importantly, post-BCAS treatment with TJ-5 significantly improved learning and memory performance, supporting the therapeutic potential of targeting IL-18/MyD88 signaling in VCID. **Conclusion:** These findings demonstrate that BCAS-induced IL-18 promotes reactive astrogliosis through MyD88-dependent NF-κB activation, contributing to white matter injury and cognitive impairment in VCID. Targeting the IL-18/MyD88 signaling axis may therefore represent a promising therapeutic strategy for VCID.

Disclosures: M. Sultan: None. **M. Habib:** None. **M. Rahman:** None. **S. Kundu:** None. **B. Sarker:** None. **I. Jahan:** None. **M. Bhuiyan:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.01/Y11

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Pioneer Award DP1 NSI06665
NIH MSTP T32GM007753
NIH T32AG000222
NIH F30HD113352
Allen Frontiers Group
Swiss National Science Foundation
Travis Roy Foundation
Massachusetts SCI Research Trust

Fondation Jean-Jacques et Felicia Lopez-Loreta pour excellence académique
HCBI Simmons Award

Title: Regenerating corticospinal neurons partially recapitulate growth cone molecular machinery of developing corticospinal neurons

Authors: *M. A. VICENT, A. ENGMANN, J. FROBERG, D. TILLMAN, K. NAIRN, D. NGUYEN, O. DURAK, J. D. MACKLIS;
Harvard Univ., Cambridge, MA

Abstract: Corticospinal neurons (CSN) are excitatory projection neurons that enable voluntary movement and dexterous motor control. During development, CSN extend axons to the brainstem and spinal cord to establish precise circuitry. Spinal cord injuries (SCI) that damage CSN axons cause critical and irreversible loss of motor function due to lack of CSN regeneration. Neurons are highly polarized cells with compartmentalized functions, containing multiple distinct subcellular transcriptomes and proteomes specialized for those functions. For example, local protein synthesis of axon-enriched transcripts is required for directional responses to some guidance cues. However, the composition and regulation of subtype-specific growth cone (GC)-enriched molecular machinery are essentially unknown. Investigation of animal models of increased CSN regeneration, e.g. *Pten* deletion, has not led to substantial translational progress for humans with SCI, partly due to lack of mechanistic understanding of axon and GC-localized processes enabling regeneration of mature neurons through inhibitory environments. We employ neuronal subtype-specific labeling, biochemical fractionation, and fluorescent small particle sorting for transcriptomic, translatomic, and proteomic analyses of CSN-specific GCs and somata at distinct developmental stages as well as after thoracic SCI. This enables investigation of dynamic regulation of subcellular CSN molecular machinery in response to changing, complex, *in vivo* environments, both during development and in response to injury. Multiomic analyses of CSN somata across developmental stages identify suites of genes regulated transcriptionally and post-transcriptionally as neurons transition from early, axon-elongating growth phenotypes to later, innervating/branching phenotypes. Compared to soma transcriptomes, we identify that CSN GC transcriptomes encode, on average, smaller proteins with fewer transmembrane domains. This suggests a logic for the distribution of subcellular transcriptomes that might be generally employed by other neuronal subtypes. Additionally, we find that approximately half the transcripts enriched in regenerating CSN GCs are also enriched in one or more stages of developing CSN GCs. This suggests that molecular mechanisms of axon development and/or maintenance are reused during regenerative growth, while the adult, injured cord also constrains regenerating CSN to employ other, distinct mechanisms for regeneration. Investigation of both convergent and divergent molecular mechanisms of regenerative growth offers promise toward discovery of targeted therapies for SCI.

Disclosures: M.A. Vicent: None. **A. Engmann:** None. **J. Froberg:** None. **D. Tillman:** None. **K. Nairn:** None. **D. Nguyen:** None. **O. Durak:** None. **J.D. Macklis:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.02/Y12

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSFC Grant 82371378
NKRDPC Grant 2024YFA1108200

Title: Staged DNA Methylation Remodeling Following Spinal Cord Injury: Profiling the Temporal Dynamics and Functional Significance of Non-CpG Hypomethylation

Authors: *D. LI[1,2], M. LI[2], Y. WANG[2], Z. WU[2], L. CHENG[2];
[1]Tongji Hosp. Affiliated to Tongji Univ., Shanghai, China; [2]Div. of Spine, Dept. of Orthopedics, Tongji Hosp. Affiliated to Tongji University, Sch. of Medicine, Tongji Univ., Shanghai, China

Abstract: Spinal cord injury (SCI) induces transcriptional and epigenomic remodeling. However, the temporal characteristics, genomic distribution, and functional significance of injury-associated DNA methylation alterations remain incompletely elucidated. In this study, we conducted profiling of cytosine methylation in adult female C57BL/6 mice subsequent to T9 contusion SCI. Reduced-representation bisulfite sequencing was employed on lesion-centered spinal cord samples obtained from sham mice and at seven post-injury time points (days 0, 1, 3, 7, 14, 28, and 42). SCI led to a modest yet significant reduction in global methylation, which was primarily attributed to non-CpG methylation at CHG/CHH sites rather than CpG methylation. Non-CpG cytosines were abundant in sequence contexts but accounted for only a small proportion of genome-wide methylated cytosines, rendering their post-injury loss a selective signal. Hierarchical clustering and principal component analysis distinguished early (days 0-3), intermediate (days 7-14), and late (days 28-42) methylation states. The greatest loss of total cytosine methylation and non-CpG methylation occurred at the intermediate stage. Across promoters, 5' and 3' untranslated regions, exons, and introns, CpG methylation remained largely stable, whereas CHG and CHH methylation were extensively reduced after SCI. Genome-wide profiling of 26,816 genes revealed comparable methylation landscapes across CpG, CHG, and CHH contexts. However, injury-associated differential methylation regions (DMRs) were enriched in intronic, intergenic, and repetitive elements. Non-CpG DMRs remained hypomethylated until day 14 and partially recovered thereafter. Promoter DMR annotation associated methylation dynamics with synaptic organization, neuronal projection formation, axon guidance/regeneration, spinal cord development, and developmental signaling pathways, but not with canonical glial activation, inflammation, or angiogenesis terms. Integration with RNA-seq data demonstrated inverse relationships between promoter/intron CpG methylation and gene expression, as well as between CHG/CHH methylation across promoters, exons, and introns and transcription. These findings delineate staged DNA methylation remodeling following SCI and identify non-CpG hypomethylation as an epigenomic feature associated with regenerative and synaptic gene programs.

Disclosures: D. li: None. **M. Li:** None. **Y. Wang:** None. **Z. Wu:** None. **L. Cheng:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.03/Y13

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Targeted Reversal of Epigenetic Constraints for Spinal Cord Repair

Authors: *A. MENON, M. KUMARAN, D. KESIREDDY, N. KRISHNA, Y. SAHU, I. VENKATESH;
CSIR-CCMB, HYDERABAD, India

Abstract: Axonal tracts of the Central Nervous System (CNS) ferry signals between the Brain and Body and are indispensable for proper nervous system function. Injury disrupts this communication, leading to permanent loss of movement and sensation in adult mammals. Transcription Factors (TFs) are required for the precise activation of Regeneration-associated genes (RAGs) to initiate repair. However, a prerequisite for TF binding is accessible chromatin, which adult CNS neurons lack. We and others have shown that global remodelling of this inaccessible landscape yields minimal growth. Thus, regeneration demands a fundamentally different approach: targeted chromatin unlocking at RAG loci, a strategy lacking in the field. To address this, we have identified a novel class of TFs that directly reverses chromatin constraints at RAG loci in injured adult neurons. This targeted remodelling achieves 5-fold selective chromatin accessibility at regulatory regions, accompanied by an 11.6-fold increase in active enhancer mark and reorganisation of the 3D genome topology. These changes reposition RAG domains toward transcriptionally active compartments and reactivate gene networks essential for axonal regeneration. Together, our findings reveal that regenerative failure in the adult CNS is not irreversible, but epigenetically constrained. By selectively unlocking silenced regenerative chromatin programs, these factors convert injured CNS neurons into a more developmentally permissive state, establishing targeted epigenomic reprogramming as a powerful therapeutic strategy for spinal cord injury and other CNS disorders. To enhance these effects, we are testing combinatorial treatments pairing these factors with pro-regenerative TFs and additional chromatin remodelers, with the goal of promoting recovery after spinal cord injury and other CNS disorders.

Disclosures: A. Menon: None. **M. Kumaran:** None. **D. Kesireddy:** None. **N. Krishna:** None. **Y. Sahu:** None. **I. Venkatesh:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.04/Y14

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSFC Grant 82371378
NKRDPC Grant 2024YFA1108200

Title: AEP-mediated Tau fragmentation and spreading causes neuronal loss through the dural lymphatic drainage after spinal cord injury

Authors: ***Y. WANG**[1,2], M. LI[2], D. LI[2], Z. WU[2], L. CHENG[2];
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[2]Div. of Spine, Dept. of Orthopedics, Tongji Hosp. Affiliated to Tongji University, Sch. of Medicine, Tongji Univ., Shanghai, China

Abstract: Spinal cord injury (SCI)-induced neuron loss in brain remains incompletely defined. We demonstrated that SCI-induced asparagine endopeptidase (AEP) activation promotes tau fragmentation and the generation of neurotoxic Tau N368. This proteolysis is associated with Tauopathy spreading and neuron loss in regions beyond the lesioned spinal cord, such as the hippocampus and cortex. We further hypothesized that Tau N368 propagates through the meningeal lymphatic system. In an intact wild-type mouse model, atto488-labeled Tau N368 pre-formed fibrils (PFFs) underwent retrograde propagation, reaching the locus coeruleus, cortex, and hippocampus. Immunofluorescence further showed that PROX1, a meningeal lymphatic endothelial marker, was expressed in the tubular structures of the spinal dura and colocalized with Atto488/Tau N368 signals. In a mouse T9 contusion SCI model, PROX1, as well as AEP and Tau N368, were upregulated around the lesion site. In parallel, LRP1, a Tau uptake and transport receptor, was broadly expressed in the spinal parenchyma and spatially associated with Tau N368. These findings support the idea that SCI-induced neuron loss in the brain might be related to the spread of Tau N368 fibrils through LRP1-associated parenchymal uptake and dural lymphatic-associated drainage, ultimately contributing to hippocampal and cortical neuronal loss.

Disclosures: Y. wang: None. **M. Li:** None. **D. Li:** None. **Z. Wu:** None. **L. Cheng:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.05/Y15

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: the Science and Engineering Research Board
CSIR
CSIR-CCMB

the Department of Biotechnology (DBT)
), the Anusandhan National Research Foundation (ANRF)

Title: Nuclear Receptor Transcription Factors promote axon regeneration following spinal cord injuries

Authors: *Y. SAHU[1], A. NARAYAN PS[2], M. KUMARAN[3], D. KESIREDDY[1], A. SUKUMAR[1], A. MENON[4], I. VENKATESH[1];
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Abstract: Spinal cord injury (SCI) results in permanent loss of motor function due to the regenerative failure of corticospinal tract (CST) axons, a critical barrier limiting functional recovery. While intrinsic manipulation can drive regrowth, the entire set of transcription factors (TFs) required for robust regeneration remains vastly incomplete. By systematically evaluating developmental gene networks supportive of growth, we identified a group of factors belonging to the nuclear receptor family. Overexpression of these developmental TFs singly and in combination significantly promoted in vitro neurite outgrowth. To evaluate their therapeutic potential in vivo, we utilized viral-mediated gene delivery to target mature layer 5 motor cortex CST neurons in adult mice subjected to a thoracic spinal cord crush injury. In vivo, transcription factor overexpression drove robust CST axon regeneration across and distal to the injury epicenter, overcoming the intrinsic regenerative limitations of mature corticospinal neurons. Critically, this anatomical regeneration correlated with significant functional improvements in motor performance, including enhanced hip-rise, grip strength, and normalized gait kinematics, as quantified through DeepLabCut-based behavioural analysis. Multi-omic profiling of regenerating CST neurons revealed a previously uncharacterized mechanism whereby Nuclear Receptor transcription factors promote regeneration through coordinated transcriptional repression and buffering of injury-induced cellular stress pathways. By maintaining cellular homeostasis during protracted regenerative growth, these factors sustain axon elongation and facilitate functional recovery following SCI. Our results identify a developmental Nuclear Receptor transcription factor network as a potent regulator of CST regeneration and establish this transcription factor family as a potential therapeutic target for functional restoration after spinal cord injury.

Disclosures: Y. Sahu: None. **A. Narayan PS:** None. **M. Kumaran:** None. **D. Kesireddy:** None. **A. Sukumar:** None. **A. Menon:** None. **I. Venkatesh:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.06/Y16

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity
Robert Campeau Family Foundation
Dr. C.H. Tator Chair in Brain and Spinal Cord Research at UHN

Title: Defining The Molecular and Functional Consequences of Apolipoprotein E4 After Spinal Cord Injury

Authors: *Y. CHAMPIRI[1], T. MIMURA[3], J. HONG[2], A. ASGARIHAFSHEJANI[2], Z. PATEL[1], L. DABIJA[4], C. M. ZHOU[1], A. ZARRINE-AFSAR[4], M. V. SOFRONIEW[5], M. G. FEHLINGS[6];
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Abstract: Spinal cord injury (SCI) results in profound motor dysfunction, reducing the quality and quantity of life. Although treatments have aimed at restoring function by bridging the lesioned circuits, certain genetic factors undermine functional recovery, namely Apolipoprotein E (APOE), a tri-allelic (E2, E3, E4) gene. Emerging evidence has demonstrated that humans heterozygous for the E4 gene exhibit limited functional recovery following SCI. The central goal of this project was to identify the underlying molecular mechanisms by which APOE4 disrupts astrocyte function following thoracic SCI, and to evaluate the subsequent functional consequences. Using a bilateral thoracic clip contusion-compression SCI model in humanized APOE4 and APOE3 knock-in with astrocyte-specific conditional knockout mice, we mapped the mechanisms by which APOE4 impacts recovery. We employed single-nucleus RNA sequencing and MALDI mass spectrometry imaging to determine cell-type-specific transcriptional reprogramming and lipidomic dysregulation within the lesion microenvironment. Behavioural and electrophysiological assessments evaluated the consequent functional outcomes across genotypes. Our results showed that astrocytic APOE4 drove pro-inflammatory transcription, peripheral immune cell infiltration, and impaired lipid homeostasis at the site of injury, and its removal partially rescued locomotor recovery, normalized corticospinal conduction, and reduced excitatory/inhibitory synaptic imbalance. These findings will establish the APOE genotype as a determinant of SCI recovery and identify potential therapeutic targets to enhance functional recovery.

Disclosures: Y. Champiri: None. **T. Mimura:** None. **J. Hong:** None. **A. Asgarihafshejani:** None. **Z. Patel:** None. **L. Dabija:** None. **C.M. Zhou:** None. **A. Zarrine-Afsar:** None. **M.V. Sofroniew:** None. **M.G. Fehlings:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.07/Y17

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

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

Title: Distribution and Toxicity of BDNF-derivatized Nanoparticles Delivering C3 Transferase to Rat Spinal Cord

Authors: *P. CHIU[1], S. GHOSH[2], D. L. HYNDS[1];
[1]Biol., Texas Woman's Univ., Denton, TX; [2]Southeast Missouri State Univ., Cape Girardeau, MO

Abstract: Traumatic spinal cord injury can disrupt sensory, motor, and autonomic functions, and any damage can lead to permanent disability. Much dysfunction can be attributed to damaged axons ascending or descending in the spinal cord, and promotion of function axon regeneration may be an ideal way to enhance functional recovery. Axon regeneration is inhibited by axon growth repellents released by disrupted myelin and during glial scar formation. Many inhibitors activate the Ras homolog family member A (RhoA), which regulates axon growth by pausing axon initiation and activating myosin II. C3 transferase is a RhoA inhibitor that increases axon regeneration and promotes function recovery in rodent spinal cord injury models. However, clinical trials using a derivatized version of C3 do not indicate increased functional recovery, perhaps because an effective dose cannot be delivered to damaged neurons. We have designed a series of nanomaterial hydrogels that are surface functionalized to target specific cells and to release therapeutic on demand. When surface-functionalized with brain-derived neurotrophic factor (BDNF), our nanospheres cross a model of the blood brain barrier (BBB), are preferentially taken up by corticospinal tract neurons in culture, and increase neuronal process extension on triggered release of C3 transferase. In the next step in this study, we have injected nanomaterial drug delivery hydrogels intravenously in the tail vein of adult female rats and assessed the nanomaterial toxicity using increasing concentrations of hydrogels, nanomaterial distribution using live animal imaging and immunohistochemistry, and efficacy to support regeneration across a spinal cord hemisection. Results from these experiments may identify an effective paradigm for delivering C3 transferase to promote functional recovery in human acute and chronic spinal cord injury.

Disclosures: P. Chiu: None. **S. Ghosh:** None. **D.L. Hynds:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.08/Y18

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Pioneer Award DP1 NSI06665
Travis Roy Foundation
NIH T32AG000222
NIH F30HD113352
Fondation Jean-Jacques et Felicia Lopez-Loreta pour excellence académique
HCBI Simmons Award
NIH MSTP T32GM007753
Allen Frontiers Group
Massachusetts SCI Research Trust

Title: Targeted motor cortex overexpression of pluripotency transcription factors Oct4, Sox2, and Klf4 reduces retraction of corticospinal neuron axons following spinal cord injury

Authors: *K. NAIRN, M. A. VICENT, A. ENGMANN, M. ROSS, J. D. MACKLIS; Harvard Univ., Cambridge, MA

Abstract: Corticospinal neurons (CSN) are the subtype of excitatory projection neurons whose axons connect the cerebral cortex to the spinal cord to enable voluntary and dexterous movement. Developmental axon growth is guided by subcellular structures known as growth cones (GCs), which integrate extra- and intracellular cues to maneuver complex environments, allowing CSN to connect to distant targets in the spinal cord and establish precise circuitry. After adult mammalian spinal cord injury (SCI), injured CSN axons, unlike peripheral axons, do not form functional GCs or regenerate past the lesion due to various cell-intrinsic and extrinsic factors that render the central nervous system largely nonregenerative. Work from the Zhigang He and David Sinclair laboratories demonstrated that overexpression of Oct4, Sox2, and Klf4 (OSK), three transcription factor genes associated with early pluripotent stages of embryonic development, promotes regeneration in the adult mouse optic nerve after crush injury, suggesting that in vivo partial reprogramming might enhance regeneration of other central nervous system axons. With this first investigation of OSK-induced regenerative effects after SCI, we demonstrate that OSK can be reproducibly overexpressed in CSN by targeting motor cortex via ultrasound-guided viral injections at early postnatal stages, and that CSN axons fluorescently labeled anterogradely via viral injection into the motor cortex can be visualized throughout the spinal cord. Further, six weeks after a clinically relevant clip compression SCI, OSK-overexpressing CSN exhibit significantly reduced axonal retraction from the lesion midpoint compared with non-OSK controls. We conduct further investigation via super-resolution confocal microscopy to determine whether OSK overexpression might promote additional regenerative responses, including axon sprouting rostral and caudal to the injury site and formation of retraction bulbs or regenerative growth cones at the leading ends of injured axon fibers, each of which are dynamic processes related to axon regeneration. Ultimately, this work enables future research to identify GC-specific RNA and protein molecular machinery changes associated with OSK-induced changes in axon behavior following injury, with the broader goal of progress toward regeneration-based therapeutics to treat SCI.

Disclosures: K. Nairn: None. **M.A. Vicent:** None. **A. Engmann:** None. **M. Ross:** None. **J.D. Macklis:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.09/Y19

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Department of the Army – USAMRAA HT9425-23-1-0562 (SC220248)
NuvOx Therapeutics for providing NanO2

Title: Longitudinal Multimodal Evaluation of Cervical Spinal Cord Injury Progression and Therapeutic Effects of Nanoparticle-Based Oxygen Therapy in Rats

Authors: *J. HOU[1,2], C. BROWN[2,1], D. PLANT[1], S. TSUDA[2,1], F. CHEUNG[1], A. PULLOS[2,1], K. S. KLIPPEL[2,1], F. RIVERA VAZQUEZ[2,1], A. KIDWAI[2,1], A. MONDAL[1], M. KUMAR[1], C. GARVAN[2], B. SPIESS[2], F. J. THOMPSON[1,3], P. K. BOSE[1,2,4];
[1]North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; [2]Anesthesiol., [3]Neurosci., [4]Neurol., Univ. of Florida, Gainesville, FL

Abstract: Cervical spinal cord injury (CSCI) causes severe and persistent neurological deficits. Beyond the initial mechanical trauma, injury-induced ischemia and impaired tissue oxygenation initiate secondary injury cascades involving oxidative stress, neuroinflammation, edema, and progressive degeneration of spared tissue. These processes contribute to chronic motor dysfunction, including gait and spasticity, yet effective therapies targeting early ischemic injury remain limited. $NanO_2$ (NuvOx Therapeutics, AZ) is an intravenous perfluorocarbon nanoparticle emulsion designed to enhance oxygen transport and tissue oxygenation. The objective of this study was to longitudinally characterize the progression of ischemia-associated secondary injury over 8 weeks using multimodal in vivo and ex vivo MRI, behavioral and physiological assessments of motor dysfunction and spasticity, and cellular/molecular analyses. We further tested the hypothesis that early $NanO_2$ administration attenuates ischemia-driven secondary injury, preserves spinal cord tissue integrity, and improves functional recovery following CSCI. Adult Sprague-Dawley rats received moderate $C_{6/7}$ contusive SCI (200 kdynes, IH) and were randomized to $NanO_2$ (0.6 ml/kg, i.v., 3 doses) or normal saline (NS) groups. Longitudinal *in vivo* 7T MRI was performed at 1, 4, and 8 weeks post-CSCI to quantify edema and lesion progression. Ex vivo GRE-3D quantitative susceptibility mapping measured total injury volume, while diffusion tensor imaging (DTI) assessed white matter integrity. Functional outcomes were evaluated using 3D gait analysis, CatWalk XT, velocity-dependent ankle torque, triceps surae EMG, and H-reflex rate-depression testing. Immunohistochemistry assessed inflammatory and oxidative stress markers (e.g., IL-1β, NFκB, Iba1, CD68, NT3, 4-HNE). CSCI produced progressive edema and cystic cavitation, lesion expansion, and disruption of spinal cord tract integrity. $NanO_2$ treatment significantly reduced edema and total injury volume and improved DTI indices of tissue preservation. These structural benefits were accompanied by improved locomotor performance, enhanced gait parameters, and reduced hindlimb spasticity compared with NS controls. $NanO_2$ also reduced expression of inflammatory and oxidative stress markers. Collectively, these findings demonstrate that early enhancement of oxygen delivery

mitigates ischemia-associated secondary injury, preserves spinal cord tissue, and improves functional recovery after CSCI. Targeting post-traumatic ischemia may represent a promising neuroprotective strategy for reducing long-term disability following SCI.

Disclosures: J. Hou: None. **C. Brown:** None. **D. Plant:** None. **S. Tsuda:** None. **F. Cheung:** None. **A. Pullos:** None. **K.S. Klippel:** None. **F. Rivera Vazquez:** None. **A. Kidwai:** None. **A. Mondal:** None. **M. Kumar:** None. **C. Garvan:** None. **B. Spiess:** None. **F.J. Thompson:** None. **P.K. Bose:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.10/Y20

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSFC Grant 82371378
NKRDPC Grant 2024YFA1108200

Title: An AI-screened novel TrkB small molecular agonist targeting intracellular kinase domain promotes axon regeneration and functional recovery after spinal cord injury

Authors: *M. LI[1,2], Y. WANG[2], D. LI[2], N. XIE[2], Z. WU[2], L. CHENG[2];
[1]Tongji Hosp. Affiliated to Tongji Univ., Shanghai, China; [2]Div. of Spine, Dept. of Orthopedics, Tongji Hosp. Affiliated to Tongji University, Sch. of Medicine, Tongji Univ., Shanghai, China

Abstract: Neuronal death and impaired axon regeneration are major barriers to functional recovery after spinal cord injury (SCI). Although activation of the brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway promotes neural repair, the therapeutic application of exogenous BDNF is limited by poor delivery across the blood-brain barrier. Here, we describe TJA, a novel small-molecule TrkB agonist that directly binds the intracellular domain of TrkB, distinguishing it from previously reported TrkB agonists that primarily target the extracellular receptor domain. Importantly, this new TrkB agonist was screened out based on our AI algorithm, Token-Mol 1.0, which was published in the previous work (Nat. Commun., Wang et al, 2025). Binding of TJA to the intracellular region of TrkB was confirmed by surface plasmon resonance (SPR) and molecular docking. TJA directly activated TrkB signaling in the absence of endogenous BDNF and showed no obvious activation of TrkA or TrkC, indicating its high TrkB specificity. Moreover, comparable to BDNF, TJA significantly promoted neuronal differentiation of human neural stem cells. In the mouse SCI model, oral administration of TJA significantly improved Basso Mouse Scale (BMS) scores and increased neuronal survival and axon density. Together, these findings identify TJA as a selective intracellular TrkB agonist capable of activating TrkB signaling independently of BDNF.

Disclosures: M. li: None. **Y. Wang:** None. **D. Li:** None. **N. Xie:** None. **Z. Wu:** None. **L. Cheng:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.11/Y21

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Spinal Cord Injury Research Program (SCIRP) Investigator-Initiated Research Award # SC210266 from the United States Department of Defense (DoD) Merit Review Award # B3986-R/1 I01 RX003986-01A1, from the United States Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)

Title: Targeted Iron Chelation Reduces Oxidative Stress and Improves Functional Recovery Following Cervical Spinal Cord Injury in Rats

Authors: *P. K. BOSE[1,2,3], J. HOU[1,2], S. TSUDA[2,1], D. PLANT[1], C. BROWN[2,1], F. CHEUNG[1], A. KIDWAI[2,1], A. PULLOS[2,1], K. S. KLIPPEL[2,1], A. MONDAL[1], M. KUMAR[1], R. J. BERGERON[4], F. J. THOMPSON[1,5];
[1]North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; [2]Anesthesiol., [3]Neurol., [4]Medicinal Chem., [5]Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Cervical spinal cord injury (C-SCI) produces persistent motor deficits, spasticity, and reduced quality of life. Following the primary insult, hemorrhage-derived free iron accumulates within the injured spinal cord, disrupting blood-spinal cord barrier (BSCB) integrity and promoting oxidative stress, neuroinflammation, and progressive neurological deterioration. Targeting iron-mediated secondary injury may therefore provide a novel therapeutic strategy for SCI. We evaluated the efficacy of SP420, a novel, targeted iron chelator, in a rat model of contusive C-SCI and tested the hypothesis that acute and chronic post-injury iron chelation reduces secondary injury and improves functional recovery.Adult SD rats received moderate $C_{6/7}$ contusive SCI (200 kdynes) and were randomized to SP420 or saline treatment. SP420 (66 mg/kg, s.c.) was initiated either acutely or chronically after injury and administered on alternating days for two weeks. Functional outcomes included assessments of spasticity, gait, and descending motor pathway function. Imaging measures included T1/T2-weighted MRI, susceptibility-weighted imaging, quantitative susceptibility mapping (QSM), and diffusion tensor imaging (DTI). Histological and immunohistochemical analyses quantified iron deposition, oxidative stress, inflammation, BSCB integrity, and neural tissue preservation. Safety assessments included behavioral observations, hematology, and liver and kidney function. $C_{6/7}$ SCI produced marked increases in velocity-dependent ankle torque and stretch-evoked EMG responses, indicating spasticity. SP420 significantly reduced spasticity in both treatment

paradigms, with greater effects following acute administration. Treated animals also exhibited improved locomotor performance and interlimb coordination compared with saline-treated SCI controls. SP420 reduced iron-associated oxidative stress and neuroinflammatory responses, evidenced by decreased expression of reactive oxygen species markers and IL-1β. Histological analyses revealed reduced iron accumulation, while in vivo and ex vivo DTI demonstrated improved integrity of corticospinal and rubrospinal pathways. No adverse safety effects were detected. These findings identify iron-mediated oxidative stress and neuroinflammation as key contributors to chronic dysfunction after C-SCI and demonstrate that targeted iron chelation mitigates these pathological processes. By reducing secondary injury, preserving motor pathways, and improving recovery, SP420 shows strong translational potential as a mechanism-based therapy for both acute and chronic SCI.

Disclosures: P.K. Bose: None. **J. Hou:** None. **S. Tsuda:** None. **D. Plant:** None. **C. Brown:** None. **F. Cheung:** None. **A. Kidwai:** None. **A. Pullos:** None. **K.S. Klippel:** None. **A. Mondal:** None. **M. Kumar:** None. **R.J. Bergeron:** None. **F.J. Thompson:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.12/Y22

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NINDS #2R01NS097880-06 A1
NeuroHope Therapeutics, Inc.

Title: Effect of Local and Sustained Dexamethasone Delivery by PgP Nanocarrier on Motor Function and Secondary Injury in a Rat Thoracic Contusion SCI Model

Authors: *A. VANDENBERG[1], H. SHIN[1], S. YANG[1], D. GONZALEZ[2], M. LEFEVRE[1], K. WEBB[1], M. R. DETLOFF[3], J. LEE[1];
[1]Bioengineering, Clemson Univ., Clemson, SC; [2]NeuroHope Therapeut., Piedmont, SC; [3]Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Spinal cord injury (SCI) is a devastating neurological disorder that disrupts critical neuronal networks, often resulting in permanent motor and sensory deficits. Beyond the initial mechanical insult, SCI triggers a complex secondary injury cascade including edema, oxidative stress, extensive immune cells infiltration, and progressive tissue degeneration. Corticosteroids such as dexamethasone (DX) have demonstrated potent anti-inflammatory effects and the ability to attenuate secondary injury following SCI by suppressing pro-inflammatory signaling pathways and reducing immune cell infiltration. Despite these therapeutic benefits, the clinical utility of DX remains limited due to adverse effects associated with high dose systemic administration. Consequently, targeted drug delivery strategies that localize DX to the injury site

while minimizing off-target toxicity are essential to realize the therapeutic potential of DX. In our lab, we developed an amphiphilic co-polymer, poly(lactide-co-glycolide)-graft-polyethylenimine (PgP, US Patent 10,232,050 B1) capable of providing local, sustained delivery of DX for the treatment of SCI. The objective of this study is to evaluate the therapeutic efficacy of DX loaded PgP (DX-PgP) via intrathecal administration on motor function, neuropathic pain, and secondary injury in a rat acute moderate thoracic contusion SCI model. DX was loaded in PgP by solvent evaporation method and loading efficiency of DX was measured by HPLC system. A moderate T9 contusion SCI model was generated in Sprague-Dawley rats and intrathecal catheters inserted at the lumbar level (L4-5). Animals were divided into 3 groups: 1) Normal, 2) untreated SCI (saline) and 3) DX-PgP (4 μg DX). Immediately after injury, DX-PgP or saline was administered via intrathecal catheter using a microinjection pump with Hamilton syringe (28 G). Locomotor function and neuropathic pain were evaluated weekly up to 6 weeks post-injury (WPI) using BBB scoring system and von Frey test, respectively. We observed that the DX-PgP treatment group showed slightly higher BBB scores compared to untreated SCI group. For neuropathic pain, DX-PgP treated rats exhibited slightly higher withdrawal thresholds than untreated SCI rats even though the difference was not significant. Rats were sacrificed via cardiac perfusion at 6 WPI and histological analysis is on going. These initial results suggest that localized, low-dose DX delivery can improve motor recovery and reduce neuropathic pain after SCI.

Disclosures: A. Vandenberg: None. **H. Shin:** None. **S. Yang:** None. **D. Gonzalez:** None. **M. LeFevre:** None. **K. Webb:** Other; Co-Founder and hold equity in NeuroHope Therapeutics, Inc. A small business seeking to develop PgP-based nanotherapeutics for neurotrauma. **M.R. Detloff:** None. **J. Lee:** Other; Co-Founder and hold equity in NeuroHope Therapeutics, Inc. A small business seeking to develop PgP-based nanotherapeutics for neurotrauma.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.13/Y23

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Craig H. Neilsen Grant 1348482

Title: Localized Delivery of a MMP Inhibitor to Improve Bladder Function After Spinal Cord Injury

Authors: *A. ROMERO LOZANO[1], W. HE[1], W. J. CLEVELAND[2], M. H. DONOVAN[2], A. D. GAUDET[2,3], L. J. NOBLE-HAEUSSLEIN[2,3], H. WANG[1];
[1]Biomed. Engin., [2]Neurol., [3]Psychology, Univ. of Texas at Austin, Austin, TX

Abstract: Beyond the initial trauma to the spinal cord, spinal cord injury (SCI) elicits multiple secondary complications, including those related to motor, bladder, sexual and bowel dysfunction. Loss of bladder function is consistently ranked as a top priority by individuals with SCI in regaining independence and improving quality of life. Previous studies have demonstrated the upregulation of matrix metalloproteinases (MMPs) in the bladder after SCI that coincides with abnormal remodeling of the bladder wall. Although the MMP inhibitor, GM6001, improves locomotor and bladder function after SCI, systemic administration of GM6001 increases the risk of adverse off-target effects. Here, we circumvent this risk by using a novel method for spatiotemporally precise drug delivery to selectively release GM6001 into the bladder after SCI. This innovative approach involves hydrogen-bonded organic frameworks (HOFs) that release cargo in response to focused ultrasound (FUS). Male mice were subjected to a T9 contusion injury and given a tail-vein injection of GM6001-loaded HOFs (HOF@GM) with subsequent FUS three times in the first 48 hours after injury. Bladders from these mice at day 2 post injury demonstrated decreased MMP2 activity compared to mice that received empty HOF nanoparticles and FUS (n=4 per group), suggesting that our approach successfully delivered functional GM6001 in the bladder. Additionally, administration of HOF@GM without FUS did not result in a reduction of MMP activity, indicating that GM6001 is not getting released without the presence of FUS (n=4 per group). A 6-week SCI study was then conducted to assess if ultrasound-triggered release of HOF@GM improved long-term voiding outcomes as measured by awake cystometry. Mice that received HOF@GM and FUS in the first 48 hours had a decreased frequency of non-voiding contractions and lower bladder weights (n=7-8 per group). These encouraging results suggest that local ultrasound-triggered release of GM6001 into the bladder wall attenuates its abnormal remodeling and hypertrophy, while reducing the risk of systemic off-target effects. This novel method of local drug delivery holds promise for the SCI community for restoring bladder function.

Disclosures: A. Romero Lozano: None. **W. He:** None. **W.J. Cleveland:** None. **M.H. Donovan:** None. **A.D. Gaudet:** None. **L.J. Noble-Haeusslein:** None. **H. Wang:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.14/Y24

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R01NS131806

Title: REV-ERB activation via SR9009 drives sex-specific modulation of anti-inflammatory transcriptional programs after spinal cord injury

Authors: *S. M. ALMAN[1,2], J. C. ALDRICH[1,2], F. C. BREMNER[1,2], U. P. KANDJOZE[3], A. R. SCHEINFELD[1,2], L. K. FONKEN[4], A. D. GAUDET[1,2,5];

[1]Dept. of Psychology, [2]Dept. of Neurol., [3]Interdisciplinary Neurosci. Program, [4]Div. of Pharmacol. and Toxicology, [5]Dept. of Neurosurg., The Univ. of Texas at Austin, Austin, TX

Abstract: Spinal cord injury (SCI) causes a cascade of neuroinflammatory effects driven by resident microglia in the central nervous system and peripherally-recruited immune cells that rely on circadian signaling for activation. One component of the transcriptional circadian clock loop, REV-ERB, suppresses pro-inflammatory gene expression, and therefore serves as an intriguing target to ameliorate SCI-elicited neuroinflammation. Here, we hypothesize that systemically administering a REV-ERB agonist, SR9009, will attenuate neuroinflammation in male and female mice after SCI. Adult male and female C57BL/6J mice were subjected to a T9 laminectomy and contusion SCI. Mice received their first dose of SR9009 at 3-hours after SCI, then were treated daily until tissue collection at 3 days post-SCI. Transcriptional analyses of spinal cord epicenters revealed that SR9009 treatment significantly suppressed SCI-induced inflammatory gene expression in female mice only, whereas male mice displayed little or no response. To establish whether male mice respond to SR9009 at higher doses, we tested whether administering a double dose of SR9009 treatment after SCI would produce a comparable response to females. Accordingly, we observed a modest anti-inflammatory effect with patterns mirroring that observed in females. We then used a lipopolysaccharide-induced neuroinflammation model to further elucidate the mechanistic underpinnings driving this notable sex-divergent response. Here, we observed that male mice that received SR9009 treatment displayed a significant, and strikingly similar, anti-inflammatory response pattern to female mice, suggesting that SR9009 dampens pro-inflammatory pathways similarly in both sexes, with particularly robust transcriptional effects in females. Future studies should explore sex-specific mechanisms and benefits of REV-ERB activation to identify new translatable approaches for improving SCI repair.

Disclosures: S.M. Alman: None. **J.C. Aldrich:** None. **F.C. Bremner:** None. **U.P. Kandjoze:** None. **A.R. Scheinfeld:** None. **L.K. Fonken:** None. **A.D. Gaudet:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.15/Y25

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R01NS131806

Title: Activation of the circadian protein REV-ERB suppresses neuroinflammation and monocyte recruitment after spinal cord injury in female mice

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Abstract: Following spinal cord injury (SCI), resident microglia and infiltrating monocyte-derived macrophages (MDMs) drive a prolonged neuroinflammatory response that exacerbates secondary damage and impairs recovery. One promising approach for reducing secondary damage is by targeting the protein REV-ERB—a circadian transcriptional repressor that suppresses inflammatory gene expression both directly and indirectly through interactions with the circadian activator BMAL1. Here, we tested whether pharmacological activation of REV-ERB with the agonist SR9009 suppresses neuroinflammation and reduces MDM recruitment after SCI. Adult C57BL/6J mice of both sexes (2-3 months old; n = 8-11 per group per sex) received a thoracic (T9) contusion SCI and were treated with SR9009 (100 mg/kg, i.p.) or vehicle daily. Bulk 3' RNA-seq of spinal cord tissue at 3 days post-injury (dpi) revealed that SR9009 broadly suppressed genes related to leukocyte activation and migration in females, with minimal transcriptomic changes in males. SR9009 drove coordinated downregulation of chemokines and receptors mediating MDM recruitment including *Ccl2, Ccl7, Ccl12* in females. Gene set enrichment analysis (GSEA) confirmed enrichment of known REV-ERB target and BMAL1-dependent gene sets among SR9009-downregulated genes, consistent with on-target REV-ERB-mediated repression. SR9009 also upregulated synaptic function-related genes in females, suggesting a neuroprotective effect. To directly assess MDM infiltration, we used *Ccr2-CreERT2; Ai9-tdTomato* mice to lineage-trace circulating monocytes (labeling efficiency ~90% by flow cytometry; n = 6-8). At 7 dpi, tdTomato$^+$ MDMs were quantified at the lesion via IHC (blind to treatment and sex). SR9009 reduced MDM accumulation in females with minimal effects in males. Notably, vehicle-treated females exhibited a higher baseline MDM infiltration compared to males, suggesting a sex difference in peripheral immune cell recruitment to the injured cord irrespective of treatment. These results demonstrate that REV-ERB activation suppresses post-SCI neuroinflammation in a sexually dimorphic manner, with convergent transcriptomic and cellular evidence implicating reduced *Ccl2/Ccr2*-dependent MDM recruitment as a potential mechanism.

Disclosures: J.C. Aldrich: None. **S.M. Alman:** None. **F.C. Bremner:** None. **U.P. Kandjoze:** None. **A.R. Scheinfeld:** None. **L.K. Fonken:** None. **A.D. Gaudet:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.16/Y26

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: DoD Grant HT9425

Title: The perils of treating hypotension after SCI: When do pharmacological treatments have an adverse effect?

Authors: *A. TREVINO[1], V. BALENTINE[1], T. JOHNSTON[2], J. W. GRAU[1];
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Abstract: An adverse effect following a spinal cord injury (SCI) is hypotension. This is often treated using the noradrenergic agonist, norepinephrine (NE). Prior work suggests that NE treatment can have an adverse effect when given a day after injury, leading to a lasting impairment in behavioral function and increased tissue loss (CITE). The current study explores the circumstances under which NE treatment has an adverse effect and whether a non-noradrenergic drug (dopamine) provides an effective alternative. Male Sprague-Dawley rats received a moderate T10-T11 contusion injury in both experiments. For the dopamine (DA) experiment, baseline locomotor performance and blood pressure were assessed 24 hours after surgery. Following baseline assessment, subjects received a subcutaneous injection of 1mg/kg DA, 5mg/kg DA, or vehicle. Locomotor and blood pressure assessments were then conducted hourly for three hours. Administration of dopamine had a hypertensive effect when given a day after injury and also disrupted locomotor function. For the NE experiment, animals were allowed to recovery from surgery for four days before experimentation. Baseline locomotor performance and blood pressure were assessed before administering 0.5 mg/kg of NE or vehicle. Locomotor and blood pressure assessments were then conducted hourly for three hours. Once experimentation concluded for both experiments, a 1-cm portion of the spinal cord encompassing the site of injury was collected and assayed for hemoglobin using a Drabkin assay. When given within the first 24 hours, NE produced an acute loss in function, which was accompanied by increased hemorrhage when given immediately (30 min) after injury. No adverse effect was observed when the drug was given 4 days after injury. The results suggest caution in the treatment of hypotension within the first 48 hours of injury and that the adverse effect of drug treatment may be related to the surge in blood pressure.

Disclosures: A. Trevino: None. **V. Balentine:** None. **T. Johnston:** None. **J.W. Grau:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.17/Y27

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Neilsen Grant 1000927

Title: The Benzodiazepine Midazolam Counters the Adverse Effect of Noxious Stimulation After SCI

Authors: *C. T. PHINNEY[1], J. ABRAHAM[2], N. KOBAYASHI[1], J. W. GRAU[1];
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Abstract: Previous studies have shown that noxious stimulation following spinal cord injury (SCI) can significantly impair locomotor recovery while increasing hemorrhage, inflammation, and cell death at the injury site (Turtle, 2017, J Neurotrauma, 34, 1200). Subsequent research found that this detrimental effect could be mitigated by inducing a comatose state using the barbiturate pentobarbital (Davis, 2023, J Neurotrauma, 40, 2552). Further, maintaining a state of anesthesia with pentobarbital for 12 hours after injury reduced hemorrhage. The current study explores whether inducing sedation with the benzodiazepine midazolam has a comparable protective effect. In the first study, rats were subjected to a moderate T12 contusion injury, with groups balanced based on locomotor scores recorded 24 hours post-injury. Subsequently, they received either saline or 5 mg/kg of midazolam via intraperitoneal injection, followed by noxious electrical stimulation (shock) or nothing. Locomotor scores were reassessed 24 hours later, after the sedative effect of the drug had cleared. This step was taken because a preliminary study using 0, 1, or 5 mg/kg midazolam suggested the highest dose could have a beneficial effect, but also produced a lasting sedation that made it difficult to assess behavioral function. Midazolam had no effect on locomotor function when performance was assessed 24 hours later. Rats that had previously received noxious stimulation exhibited a decline in locomotor performance, increased hemorrhage at the site of injury, and the expression of a signal (caspase 3) linked to cell death. Pretreatment with midazolam (5 mg/kg) blocked these effects. In the second study, rats underwent a severe T12 contusion injury and then received saline or midazolam at doses of 1 mg/kg or 5 mg/kg (s.c.). These injections were administered hourly for the subsequent 12 hours. Twelve hours later, after the drug-induced sedation had waned, locomotor scores were assessed. Treatment with midazolam reduced weight loss but increased the incidence of hematuria. While a low dose (1 mg) reduced hemorrhage, as assayed by spectrophotometry and the Drabkin assay, a high dose (5 mg) had the opposite effect. A high dose also appeared to amplify the loss of locomotor function. The results suggest that treatment with a benzodiazepine can counter the adverse effect of pain after SCI, but may have an adverse effect if given soon (within hours) of injury.

Disclosures: C.T. Phinney: None. **J. Abraham:** None. **N. Kobayashi:** None. **J.W. Grau:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.18/Y28

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: AMED-241014888

Title: Crtac1B (LOTUS), an antagonist of NgR1 and PirB, promotes recovery after acute and chronic spinal cord injury

Authors: ***K. ABE**[1,2], J. MATSUBAYASHI[2], K. KOBAYASHI[2], Y. KAWAGUCHI[2], K. TAKEI[2];
[1]Yokohama-city university, Yokohama, Japan; [2]Dept. of Neurol. and Stroke Med., Yokohama-City Univ., Yokohama, Japan

Abstract: Regeneration of the central nervous system (CNS) after spinal cord injury (SCI) is severely limited. Following SCI, multiple axon growth-inhibitory factors derived from myelin debris and glial scar tissue interact with Nogo receptor 1 (NgR1) and paired immunoglobulin-like receptor B (PirB), thereby suppressing axonal regeneration and functional recovery. Thus, effective therapeutic strategies require both inhibition of these receptors and promotion of axonal regrowth and synapse formation beyond the lesion site. Crtac1B, also known as lateral olfactory tract usher substance (LOTUS), functions as an endogenous antagonist of both NgR1 and PirB. LOTUS plays essential roles in axonal tract formation during development and in promoting axonal regrowth and synaptogenesis in the adult CNS. However, LOTUS expression is markedly downregulated after SCI, and this reduction is thought to contribute to impaired neural repair and delayed functional recovery. We previously demonstrated that transgenic overexpression of LOTUS enhances axonal regeneration and functional recovery following SCI. Building on these findings, we investigated adeno-associated virus (AAV)-mediated gene delivery as a clinically translatable strategy to restore LOTUS expression. Intracranial administration of AAV-LOTUS during the acute or subacute phase after SCI significantly improved motor and sensory function at 28 days post-injury, as assessed by the Basso Mouse Scale (BMS) and grid-walking test. Histological analyses revealed increased serotonergic fiber density beyond the lesion center in the raphespinal tract in AAV-LOTUS-treated mice, suggesting enhanced axonal regeneration and circuit reorganization. Furthermore, comparable functional recovery was observed even when AAV-LOTUS was administered during the chronic phase (one month post-injury). Collectively, these findings demonstrate that AAV-mediated LOTUS gene therapy promotes neural regeneration after SCI by antagonizing NgR1 and PirB signaling and compensating for the loss of endogenous LOTUS. This approach represents a promising and broadly applicable therapeutic strategy for SCI across both acute and chronic phases.

Disclosures: K. Abe: None. **J. Matsubayashi:** None. **K. kobayashi:** None. **Y. Kawaguchi:** None. **K. Takei:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.19/Y29

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (Grant number RS-2023-KH139336)

Title: Sustained Harpagoside Delivery Promotes Axonal Regeneration and Functional Recovery after Spinal Cord Injury via Ferroptosis Suppression

Authors: *J. HONG, H. KIM, W. JEON, J. LEE, C. YEO, H. KIM, I. HA;
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Abstract: Spinal cord injury (SCI) induces progressive neurodegeneration through persistent neuroinflammation, iron overload, and ferroptotic cell death, ultimately limiting functional recovery. Harpagoside (HS), a bioactive iridoid glycoside with anti-inflammatory and neuroprotective properties, has therapeutic potential, but its clinical application is limited by poor stability and rapid clearance from the injury site. Here, we developed a silk-collagen-laminin (SC-L) hydrogel incorporating HS-loaded mesoporous silica nanoparticles (HS@MSN) for sustained local delivery and investigated its therapeutic effects on SCI-associated ferroptosis. Bulk RNA sequencing revealed that ferroptosis-related alterations progressed from acute inflammatory responses to chronic iron accumulation after SCI, with the most prominent changes occurring at 1 month post-injury. HS@MSN and SC-L hydrogels were characterized by physicochemical and rheological analyses, confirming efficient drug loading and favorable injectability, self-healing, and viscoelastic properties. In a three-dimensional neuronal culture model exposed to $FeSO_4$-induced iron stress, HS@MSN-loaded hydrogels enhanced neuronal viability, promoted neurite outgrowth, and regulated genes associated with neuronal regeneration and iron metabolism. In a moderate contusion SCI model, animals treated with HS@MSN-incorporated SC-L hydrogel showed significantly improved locomotor recovery, coordination, and gait performance over 12 weeks, as assessed by Basso-Beattie-Bresnahan (BBB), ladder rung, and footprint analyses. Treatment also reduced neuroinflammation, attenuated iron accumulation and ferroptosis-related changes, and promoted neural tissue regeneration. To evaluate axonal regeneration, Thy1-EGFP transgenic rats received local implantation of the hydrogel following SCI. At 12 weeks post-transplantation, tissue clearing and light-sheet fluorescence microscopy revealed substantially enhanced axonal regrowth within the lesion area compared with SCI controls. Collectively, these findings demonstrate that sustained local delivery of HS via HS@MSN-incorporated SC-L hydrogel suppresses ferroptosis-associated neurodegeneration, promotes axonal regeneration, and improves long-term functional recovery after SCI. This multifunctional biomaterial platform represents a promising ferroptosis-targeted therapeutic strategy for spinal cord repair.

Disclosures: J. Hong: None. **H. Kim:** None. **W. Jeon:** None. **J. Lee:** None. **C. Yeo:** None. **H. Kim:** None. **I. Ha:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.20/Y30

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: A Grant-in-Aid for Specially Promoted Research from MEXT to MY (KAKENHI no. 20H05628)

Title: Corticospinal Re-routing via a Synthetic Synapse Organizer Rapidly Restores Pre-Lesion Dexterity in Spinal-Injured Macaques

Authors: *S. PEYDA[1], R. YAMAGUCHI[2,3], Y. SUN[4], K. ISA[2], S. UENO[5], K. SUZUKI[7,8], V. CHANG[8], H. SASAKURA[9], K. M. MATSUDA[7], K. KOBAYASHI[10], K. TAKEUCHI[9], H. ONOE[6,12], R. ARICESCU[8,7], M. YUZAKI[7], T. ISA[2,11,6,3];
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Abstract: Dexterous hand movements, controlled by signals from the primary motor cortex (M1) via the corticospinal tract (CST), are severely impaired following cervical spinal cord injury (SCI). Injury-related deficits are notoriously difficult to recover. Promisingly, recovery of locomotion was observed in SCI mice following intraspinal injection of CPTX - a novel synaptic organizer bridging presynaptic nerve terminals and postsynaptic AMPA receptors - by re-establishing central neural connectivity (Suzuki et al., 2020).
Building on this, we investigated whether CPTX can recover dexterous motor function in a non-human primate SCI model.Eight macaques trained in a highly dexterous reach-and-grasp task (RGT) received a C6/C7 sub-hemisection. Seven days post-SCI the animals received a one-time perilesional injection of either CPTX (n=4) or a vehicle buffer (n=4).
Over a 120-day blinded recovery period, CPTX-treated macaques demonstrated a significantly earlier recovery onset, a significantly steeper recovery curve, and less compensatory grasping behavior. All CPTX subjects reach at least a 50% RGT success rate, whereas only two vehicle subjects reached this threshold albeit later than their CPTX counterparts.
Next, utilizing markerless pose estimation (Mathis et al., 2018) and dynamic time-warping (DTW), we evaluated pre- to post-SCI movement similarity. Within one month, finger kinematics in CPTX-treated monkeys progressively and strongly aligned with pre-injury patterns, unlike vehicle controls. This suggests that CPTX significantly accelerates recovery of hand dexterity to restore pre-lesion movement patterns.
Parallel to this functional restoration we also observed extensive structural re-organization; Using AAV-DJ viral tracers injected into the M1, we found massive CST re-routing at the pyramidal decussation and across multiple cervical spinal levels. Furthermore, confocal imaging indicated that CPTX co-localizes with pre- and postsynaptic markers of excitatory synapses

throughout the gray matter of the spinal cord.
In summary, sub-acute CPTX treatment may leverage the central nervous system's latent potential for re-routing neuronal pathways, restoring lost dexterity to pre-lesion movement patterns, and accelerating hand function recovery in our translational SCI model in non-human primates.

Disclosures: S. Peyda: None. **R. Yamaguchi:** None. **Y. Sun:** None. **K. Isa:** None. **S. Ueno:** None. **K. Suzuki:** None. **V. Chang:** None. **H. Sasakura:** None. **K.M. Matsuda:** None. **K. Kobayashi:** None. **K. Takeuchi:** None. **H. Onoe:** None. **R. Aricescu:** None. **M. Yuzaki:** None. **T. Isa:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.21/Y31

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH 1R35GM156968
NIH R16GM158720

Title: Real-Time Tracking of FAK Dynamics During Axonal Regeneration in a Microfluidic Axotomy Model With a Novel Bioluminescent Biosensor

Authors: *S. SAMARATHUNGA[1], J. BAKKE[2], E. D. PETERSEN[3], O. DUBEY[4], A. KORNILOV[5];
[1]Neurosci., Central Michigan Univ., Mt Pleasant, Sri Lanka; [2]Col. of Med., Central Michigan Univ., Mount Pleasant, MI; [3]Col. of Med., Central Michigan Univ., Mt Pleasant, MI; [4]Central Michigan Univ., Mount Pleasant, India; [5]Central Michigan Univ., Mount Pleasant, MI

Abstract: Cell adhesion and locomotion are critically involved in vital physiological functions, including tissue regeneration and neural repair. The limited regenerative capacity of adult central nervous system neurons contributes to poor recovery after traumatic nerve damage, including spinal cord injury (SCI). Focal Adhesion Kinase (FAK) serves as a central regulator of these cellular mechanics, but current endpoint methodologies such as Western blotting and immunostaining fail to capture real-time, localized kinase dynamics in living cells. Consequently, the regulatory landscape of FAK activity remains incompletely mapped. To address this gap, we are developing a bioluminescent kinase sensor (BlinKS-FAK) utilizing a split-luciferase architecture that reconstitutes and luminesces upon FAK-mediated phosphorylation events. Currently, we are testing initial sensor libraries in live cells and have successfully identified candidate sensors that exhibit adhesion-dependent responses. We are now actively optimizing these constructs through structural modifications to achieve a higher signal-to-noise ratio. Once optimized, to enable high-throughput genetic screening, this sensor will be

integrated with an EL222 light-activated transcription system to create a kinase sensor driven gene circuit (BlinKS-GC), converting transient FAK activity into a stable mScarlet-I3 red fluorescent readout. We will use stable cell lines with BlinKS-GC and perform a genome-wide CRISPR knockout library, utilizing fluorescence-activated cell sorting (FACS) and next-generation sequencing to isolate and identify genes associated with diminished and enhanced FAK activity. Finally, the identified positive regulators will be evaluated in a microfluidic in vitro axotomy model, where we will monitor local FAK dynamics at regenerating axons using bioluminescent microscopy following controlled physical injury. Experimental validation in the axotomy model is anticipated to demonstrate that manipulating these candidate regulators significantly enhances axonal sprouting and regrowth distance. Ultimately, this dual-output reporter platform will bridge a critical technical gap in monitoring real-time cellular mechanics. Identifying novel regulators of FAK will advance our understanding of neural repair and reveal new molecular targets for therapeutic strategies aimed at improving recovery following spinal cord injury.

Disclosures: S. Samarathunga: None. **J. bakke:** None. **E.D. Petersen:** None. **O. Dubey:** None. **A. Kornilov:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.22/Y32

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH R01NS119475
NIH F31NS147874

Title: Validating the Use of ChAT-cre Rats and Cre-Driven Adeno-Associated Viruses to Manipulate KCC2 in Spinal Cord Injured Rats

Authors: *N. YAKAS[1], M.-P. CÔTÉ[2];
[1]Neurobio. & Anat., [2]Dept. Neurobio. and Anat., Drexel Univ., Philadelphia, PA

Abstract: Approximately 75% of individuals with spinal cord injury (SCI) develop spasticity. Underlying spasticity is the development of imbalanced excitatory and inhibitory inputs. Descending inhibitory signals are disrupted and some neurons become hyperexcitable. Following SCI, chloride homeostasis is disrupted in motoneurons; internal chloride ion concentration decreases in large part due to internalization and loss of the potassium chloride co-transporter, KCC2. As a result, inhibitory signals triggering GABA receptors lead to an influx of chloride, rendering the inhibitory signal ineffective or even paradoxically excitatory. Global upregulators of KCC2, such as CLP, have been shown to ameliorate spasticity and the recovery of motoneuronal KCC2 expression has been correlated with improvements in spasticity. This

project seeks to develop a model to study the role of motoneuronal KCC2 specifically in spasticity following SCI and investigate its role in rehabilitation.Transgenic adult Long Evans rats with cre expression in cholinergic (ChAT+) neurons were acquired for the study. To validate the efficacy of a cre-dependent shRNA knockdown AAV (AAV6-shRNA-KCC2), intact adult rats received a total of 6, 1uL, intraspinal injections spanning L2-L6, bilaterally. Rats with a complete T9 transection were used to assess the efficacy of a cre-dependent AAV driving overexpression of KCC2 (AAV6-KCC2). Injured rats were injected at the same time as injury. This would allow the AAV to undergo transduction following the SCI-induced reduction in KCC2. Injections were targeted to the ventral horn area to minimize unintended infection of medial cholinergic interneurons. Four weeks after injections, rats were perfused and spinal tissue was collected. Immunohistochemistry was performed to quantify viral expression and KCC2 expression in motoneurons. Our preliminary analysis indicates that AAV6-shRNA-KCC2 knocked-down KCC2 expression and that AAV6-KCC2 increased KCC2 expression post-SCI. Our results suggest that ChAT-cre rats may be able to be utilized to further investigate mechanisms of spasticity and rehabilitation strategies following SCI.

Disclosures: N. Yakas: None. **M. Côté:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.23/Z1

Topic: A.04. Transplantation and Regeneration

Support: The Dr. Miriam and Sheldon G Adelson Medical Research Foundation

Title: Semaphorin 6A facilitates lens injury induced optic nerve regeneration

Authors: *X.-F. ZHAO[1], Q. FENG[2], R. J. GIGER[3];
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Abstract: Mammalian retinal ganglion cells (RGCs) are unable to regenerate injured axons spontaneously, resulting in permanent visual deficits. Interestingly, robust axon regeneration can be elicited with a mild conditioning lens injury (cLI) applied prior to optic nerve damage. Although recent studies have advanced our mechanistic understanding of CNS axon regeneration, identifying extracellular factors capable of promoting axon regeneration in experimental animal models may be preferred targets for developing therapeutic strategies to promote axon regeneration in the adult human CNS. Using a mouse model of retro-orbital optic nerve crush (ONC) injury, we found that Semaphorin 6A (Sema6A) expression is strongly upregulated in a subset of RGCs at 3, 5, and 7 days post-ONC plus cLI, when compared to parallel operated sham control mice. To assess the functional significance of *Sema6a* in injured

RGCs, we generated conditional knockout (cKO, *Sema6a fl/fl; vGlut2-Cre)* mice, lacking *Sema6a* in RGCs. When subjected to ONC plus cLI, we observed a significant reduction in RGC axon regeneration when compared to wildtype controls. Notably, the total number of RGCs in cKO was significantly lower than in wildtype littermate controls, indicating that Sema6A is not only required for axon regeneration, but also for RGCs survival. To rule out potential developmental effects associated with cKO, we injected AAV2-Cre into the posterior chamber of the eyes of *Sema6a fl/fl* mice to achieve inducible knockout (iKO) selectively in adult RGCs. Importantly, iKO *Sema6a* also reduces cLI induced RGC repair. Conversely, AAV2 mediated overexpression of *Sema6a* in RGCs, combined with CNTF, promoted RGC repair when compared to parallel processed mice injected with AAV2-GFP. Ongoing studies are focusing on the function of the *Sema6a* cytoplasmic domain and its role in RGC regeneration. In summary, our research demonstrates that, in addition to its role in axon guidance and developmental circuit wiring, Sema6A also participates in cLI-mediated CNS neuron protection and axon regeneration in adult mammals.

Disclosures: X. Zhao: None. **Q. Feng:** None. **R.J. Giger:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.24/Z2

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

Support: NIH/NINDS Grant R01NS115977
PA Department of Health CURE grant : 4100083087
Alzheimer's Association Research Grant
Spastic paraplegia foundation
PA Department of Health grant : 4100089352

Title: Investigating the role of M1-spastin in axonal regeneration and repair

Authors: *S. RAMAKRISHNAN[1], L. QIANG[2];
[1]Neurobio. and Anat., Drexel Univ. Col. of medicine, Philadelphia, PA; [2]Neurobio. and Anat., Drexel Univ., Philadelphia, PA

Abstract: Mutations in the *SPAST* gene, the leading cause of Spastic Paraplegia 4 (SPG4), result in dysfunction of spastin, a microtubule (MT)-severing protein essential for axonal maintenance and regeneration. *SPAST* produces two isoforms through alternative translation initiation: the full-length M1-spastin and the shorter, more abundant M87-spastin. While M87-spastin is well characterized for its potent MT-severing activity and its essential role in cytoskeletal reorganization during axonal regeneration, the function of M1-spastin remains poorly understood, despite its involvement in endoplasmic reticulum (ER) morphogenesis and calcium

homeostasis—pathways potentially influencing axonal regeneration independent of MT severing. Using isogenic *SPAST*-knockout (KO) human induced pluripotent stem cell (hiPSC)-derived neurons, as well as cortical neuronal cultures from *Spast*-knockout mice, we investigated the role of spastin in axonal regeneration and found that spastin depletion or functional inhibition significantly impaired axonal regrowth and was accompanied by a marked reduction in neuronal activity. Notably, ectopic expression of M1-spastin in *SPAST*-knockout hiPSC-derived neurons partially restored regenerative capacity and rescued neuronal activity deficits, suggesting that M1-spastin promotes axonal regeneration through distinct, MT-severing-independent mechanisms. This effect closely mirrored the rescue observed following chemogenetic enhancement of neuronal activity in SPAST KO neurons via Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), implicating M1-spastin in neuronal activity-dependent repair mechanisms, potentially through ER-related signaling pathways. These findings establish M1-spastin as a key modulator of neuronal repair, functioning in a manner complementary to the MT-severing role of M87-spastin, and highlight isoform-specific spastin modulation as a potential therapeutic strategy for enhancing axonal regeneration in injury and diseases.

Disclosures: S. Ramakrishnan: None. **L. Qiang:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.25/Z3

Topic: A.04. Transplantation and Regeneration

Support: The Miriam and Sheldon G. Adelson Medical Research Foundation (LB)
NEI RO1EY05690 (LB)
HSCI grant on Vision Repair and Regeneration (YY)
NEI 5R21EY033550 (YY)
ARPA grant (YY under Zhigang He)
Eye and Ear Foundation of Pittsburgh (KC)

Title: Optic nerve regeneration: clinically relevant candidates identified by screening receptor-ligand pairs in adult mouse RGC cultures, injured mouse optic nerve in vivo, and human iPSC-derived retinal organoids

Authors: *Y. YIN[1,2], K. RASULEVA[1,2], K. Z. HE[1,2], K.-C. CHANG[3], L. I. BENOWITZ[1,2,3,4]; [1]Children's Hospital, Harvard Med. Sch., Boston, MA; [2]F.M. Kirby Neurobio. Center, Boston Children's Hosp., Boston, MA; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Program in Neuroscience, Harvard medical Sch., Boston, MA

Abstract: Mature mammalian retinal ganglion cells (RGCs) are unable to regenerate injured axons, and consequently, optic nerve injury results in the irreversible loss of vision. Our earlier identification of several previously unrecognized growth factors encouraged us to carry out a systematic screen of ligands to the many receptors identified through transcriptomic studies of mature mouse RGCs. Over 70 candidates were selected to screen since their direct axon growth-promoting effects on RGCs had not yet been tested. Screening was carried out in 3 different assays. The primary screening was in adult mouse RGC cultures using automated evaluation of neurite outgrowth. Positive hits were next tested in the optic nerve injury model to evaluate efficacy in promoting optic nerve regeneration in vivo. Receptor ligands showing positive effects in both assays were then tested in human iPSC-derived retinal organoids and in human neonatal cortical neuron cultures. Several previously unrecognized receptor ligands showed clear axogenic effects in human RGCs. In addition, candidates showing positive effects in all 3 assays were tested in combination with other known treatments to optimize potential translational relevance.

Disclosures: Y. Yin: None. **K. Rasuleva:** None. **K.Z. He:** None. **K. Chang:** None. **L.I. Benowitz:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.26/Z4

Topic: A.04. Transplantation and Regeneration

Support: The Miriam and Sheldon G. Adelson Medical Research Foundation (LB)
NEI RO1EY05690 (LB)
HSCI grant on Vision Repair and Regeneration (YY)
NEI 5R21EY033550 (YY)
ARPA grant (YY under Zhigang He)
Eye and Ear Foundation of Pittsburgh (KC)

Title: Platelet-derived growth factor (PDGF) promotes vigorous axon outgrowth in human iPSC-derived retinal organoids

Authors: *K. Z. HE[1,2], K. RASULEVA[1,2], K.-C. CHANG[3], L. I. BENOWITZ[1,2,3,4], Y. YIN[1,2]; [1]Boston Children's Hospital, Dept. of Neurosurg., Boston, MA; [2]F.M. Kirby Neurobio. Center, Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Program in Neuroscience, Harvard medical Sch., Boston, MA

Abstract: The optic nerve, like other CNS pathways, does not regenerate spontaneously if injured. Over the past 3 decades, a variety of treatments have been found to promote axon regeneration, mostly in rodent models, but their potential relevance to humans has remained

unclear. Here we present a modified human iPSC-derived retinal organoid culture and analysis system, and with it, discovered that PDGF has potent effects in stimulating axon outgrowth from human RGCs. Within 5 days, some of the 5 isoforms of PDGF (AA, AB, BB, CC, DD) increased total length of growing axons more than 3-fold over baseline. The responsive doses to PDGF are compared in three different culture models of human retinal organoid, adult mouse RGCs and neonatal human primary cortical neurons. In sum, we demonstrate that PDGF is a potential growth factor for human RGCs and introduce an effective model to examine the potential clinical relevance of other molecules.

Disclosures: K.Z. He: None. **K. Rasuleva:** None. **K. Chang:** None. **L.I. Benowitz:** None. **Y. Yin:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.27/Z5

Topic: A.04. Transplantation and Regeneration

Support: RGC grant CityU 11100424
RGC grant R1005-24F
HMRF grant 08193956
ITC grant ITS/099/23FP

Title: Advancing Therapeutic Treatment of Optic Nerve Neuropathy and Glaucoma by Targeting G Protein-Coupled Receptor Signaling Pathways

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Abstract: Injuries to the central nervous system (CNS) are leading causes of long-term disability worldwide. For instance, optic neuropathy triggered by ocular trauma or chronic ocular hypertension leads to optic nerve degeneration and retinal ganglion cell (RGC) apoptosis, ultimately resulting in irreversible vision loss. Unlike the CNS, the peripheral nervous system (PNS) retains the capacity to regrow after injury; however, the capacity of adult PNS regeneration is limited, and functional recovery heavily depends on the therapeutic window between injury and treatment. Therefore, accelerating axon regeneration is a crucial strategy for both CNS and PNS repair. To evaluate the regenerative potential of a novel G protein-coupled receptor (GPCR-A), we first used a mouse model of sciatic nerve crush paired with an exhaustive list of behavioral tests. Following peripheral nerve injury, loss of GPCR-A function significantly accelerated both sensory and motor functional recovery. Then, we employed two

distinct central injury models—optic nerve crush and silicone oil-induced ocular hypertension glaucoma —to evaluate visual function recovery after injury. Consistent with our peripheral findings, GPCR-A deficiency exerted profound neuroprotective effects and preserved visual function. Our findings indicated that targeting GPCR-A holds significant therapeutic value for treating peripheral nerve injuries, traumatic optic neuropathies, and glaucoma. Future directions will focus on elucidating the underlying cellular and molecular mechanisms driving these beneficial effects and evaluating the preclinical efficacy of GPCR-A antagonists through *in vivo* testing.

Disclosures: X. Chen: None. **N. Au:** None. **T. Lo:** None. **C. Ko:** None. **C.H. Ma:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.28/Z6

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant R03NS128755
AppState Office of Student Research Travel Grant
AppState Office of Student Research Research Grant

Title: Regeneration-Activated Enhancers Orchestrating CNS Axon Repair: Discovery and Functional Testing

Authors: *O. T. CARTER[1], S. P. DHARA[2], S. DIETERLE[1], S. SAMBUKUMAR[3], J. L. MATHAI[4], K. R. SVOBODA[5], M. D. LAIOSA[3], A. J. UDVADIA[1];
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Abstract: Zebrafish possess a remarkable ability to regenerate their central nervous system (CNS), unlike mammals such as mice and humans. Successful regeneration of CNS axons, including the optic nerve, requires a coordinated shift in cellular programming driven by a temporally dynamic sequence of transcription factors. Our work focuses on identifying the regulatory elements—promoters and enhancers—that orchestrate this reprogramming during optic nerve regeneration in zebrafish. We previously characterized stage-specific transcriptomic and chromatin accessibility changes accompanying axon regrowth after injury. Among early-induced transcription factors, *jun* shows rapid upregulation within 2 days post-injury, sustained expression during axon elongation, and a return to baseline as regenerated axons re-establish synaptic connections.
Using 3C-qPCR, we identified multiple upstream and downstream sequences interacting with the

jun promoter in retinal ganglion cells (RGCs). While many of the putative enhancers interact with the promoter in both control and regenerating RGCs, we discovered a 5 kb region that interacts specifically during regeneration. This sequence encompasses intronic regions of the downstream gene *si:dkey-86e18.1*, for which homologs were found only in fish and amphibians. Multiple sequence alignment of intronic sequences from *Danio rerio, Xenopus tropicalis*, and *Takifugu rubripes* using Clustal Omega revealed a highly conserved 1.4 kb region.
To functionally test this conserved subregion, we generated stable transgenic mCherry reporter lines. Two sets of lines were produced: one pairing the putative enhancer with the predicted endogenous *jun* promoter, and one pairing it with a heterologous promoter/enhancer—a truncated fugu *gap43* regulatory element previously shown to drive expression in developing, but not regenerating, RGCs. Initial analyses show developmental expression that is downregulated by 5 days post-fertilization. We will test whether expression is reinitiated after axotomy using larval optic nerve transection and adult optic nerve crush models.
In parallel, we performed Micro-C on purified RGCs to obtain a genome-wide map of chromatin looping interactions. Integration of these data with our transcriptomic and ATAC-seq datasets will enable discovery of additional regeneration-specific regulatory elements interacting with promoters of other regeneration-associated transcription factors. The long-term goal is to identify regulatory sequences suitable for gene therapy vectors to drive temporally controlled expression of pro-regenerative genes and enhance CNS axon regeneration.

Disclosures: O.T. Carter: None. **S.P. Dhara:** None. **S. Dieterle:** None. **S. Sambukumar:** None. **J.L. Mathai:** None. **K.R. Svoboda:** None. **M.D. Laiosa:** None. **A.J. Udvadia:** None.

Poster

PSTR225: Molecular and Pharmacological Mechanisms Regulating CNS Survival and Regeneration: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR225.29/Z7

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Investigating retinal ganglion cell-cell communication dynamics after optic nerve injury

Authors: *M. PROBST[1], J. MAURER[2], G. RICE[2], K. OH[2], Y. CHENG[2];
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Abstract: Optic neuropathies resulting from traumatic injury or disease cause irreversible vision loss due to the limited regenerative capacity of the central nervous system (CNS). Following optic nerve injury, retinal ganglion cells (RGCs) undergo rapid cell death and axon degeneration, leading to permanent visual impairment. Currently, no clinical treatments can restore visual function after optic nerve injury. CNS repair is restricted by both neuron-intrinsic gene-regulation and inhibitory extrinsic signals; however, the specific cell-cell interaction dynamics after optic nerve injury require further investigation. This project investigates how RGC cell-cell communication changes after optic nerve injury to identify potential therapeutic targets for

neural repair. We integrated published single-cell RNA-sequencing (scRNA-seq) datasets of retinal and optic nerve cells after optic nerve crush (ONC) injury and performed cell-cell communication analysis to identify injury-induced changes in RGC communication. In parallel, we validated a panel of retinal marker probes in retinal sections using Xenium spatial transcriptomics. CellChat analysis revealed temporal changes in communication strength between RGCs and other cell types following ONC. We identified ligand-receptor interactions predicted to mediate these incoming signals to RGCs, including 40 receptors that cluster into discrete signaling patterns. These receptors are associated with processes such as synapse assembly, cell adhesion, cell projection, and apoptosis. Notably, several receptors, such as Tnfrsf12a and Ptrps, have previously been implicated in injury response and/or inhibition of axon regeneration. Ongoing studies are focused on validating these interactions using immunostaining and spatial transcriptomics, as well as assessing therapeutic potential with small-molecule targeting. Together, these findings identify a set of injury-inducible signaling candidates that may regulate RGC survival and regeneration after optic nerve injury. Targeting injury-inducible changes in RGC ligand-receptor communication could represent a promising therapeutic strategy for promoting CNS repair and visual function after injury.

Disclosures: M. Probst: None. **J. Maurer:** None. **G. Rice:** None. **K. Oh:** None. **Y. Cheng:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.01/Z8

Topic: E.01. Somatosensation – Pain and Itch

Support: Noncommunicable Chronic Diseases-National Science and Technology Major Project (2025ZD0546200)
National Natural Science Foundation of China (82220108009)
Beijing Outstanding Young Scientist Program (JWZQ20240101023)
STI2030-Major Projects (2021ZD0201801)
National Natural Science Foundation of China (82401407, 82571362)
Capital Medical University Talent Grant (B2402)
Xuanwu Hospital Talent Convergence Program (HZ2025ZCYX001)

Title: Spinal cord microglial IGF1 drives chronic pain in Alzheimer's Disease

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Abstract: Chronic pain is common in Alzheimer’s disease (AD), but its molecular drivers remain unknown. We identify spinal cord microglial IGF1 as a key effector linking amyloid-β (Aβ) pathology to nociceptive sensitization. AD patients exhibited mechanical hypersensitivity

associated with greater amyloid burden and more severe cognitive impairment. In human AD spinal cord and in 5XFAD mice, Aβ plaques induced an IGF1-high disease-associated microglial program, with IGF1/Igf1 most strongly enriched in DAM II microglia. Spatial, ligand-receptor, and anatomical analyses identified dorsal horn excitatory neurons and primary afferent terminals as major IGF1R-positive targets, consistent with enhanced excitatory transmission and persistent pain hypersensitivity. Strikingly, local spinal, but not cortical, Aβ42 expression was sufficient to induce microglial IGF1-mediated chronic pain. Conversely, pharmacological blockade of IGF1/IGF1R signaling or microglia-specific Igf1 deletion alleviated mechanical and thermal hypersensitivity in 5XFAD mice. These findings establish spinal microglial IGF1 as a central driver of AD-associated chronic pain and a tractable therapeutic target

Disclosures: O. Chen: None. **Y. Tang:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.02/Z9

Topic: E.01. Somatosensation – Pain and Itch

Title: Arginine vasopressin reduces neuropathic pain by enhancing spinal GABAergic inhibition

Authors: *Y. YAMAMOTO[1], M. YAMANAKA[1], W. TANIGUCHI[1], N. NISHIO[1], Y. MATSUYAMA[2], T. UENO[3], R. MIYAKE[2], Y. KAIMOCHI[1], T. NAKATSUKA[4], H. YAMADA[1];
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Abstract: Introduction: Loss of inhibitory control in the spinal dorsal horn is closely associated with the development and maintenance of neuropathic pain. Arginine vasopressin (AVP) has been reported to exert analgesic effects; however, its specific modulatory effects on spinal inhibitory synaptic transmission remain unclear. **Objective:** This study aimed to clarify the cellular mechanisms by which AVP modulates inhibitory synaptic transmission in substantia gelatinosa (SG) neurons of the spinal dorsal horn and to evaluate its analgesic effects in a rat model of neuropathic pain. **Methods:** Whole-cell patch-clamp recordings were performed on spinal cord slices prepared from adult male Sprague-Dawley rats to measure spontaneous inhibitory postsynaptic currents (sIPSCs) and miniature IPSCs (mIPSCs) in SG neurons. In vivo behavioral assessments were conducted using the spared nerve injury (SNI) neuropathic pain model, with intrathecal injection of AVP administered on postoperative day 7. **Results:** Bath application of AVP (1 μM) markedly increased the frequency of sIPSCs in SG neurons. In the presence of tetrodotoxin (TTX), AVP selectively increased the frequency of GABAergic mIPSCs without altering glycinergic currents. This effect was accompanied by no significant change in mIPSC amplitude, suggesting a presynaptic mechanism. Additionally, this

enhancement was blocked by SR 49059, a V1a receptor antagonist. AVP had no significant effect on excitatory synaptic transmission. In vivo, intrathecal administration of AVP significantly attenuated both mechanical allodynia and thermal hyperalgesia in the SNI group compared with the vehicle group. **Discussion:** The increase in GABAergic mIPSC frequency without a change in amplitude indicates that AVP enhances presynaptic GABA release onto SG neurons. The blockade of this effect by SR 49059 demonstrates that AVP acts through V1a receptors. Unlike oxytocin, which modulates both GABA and glycine, AVP selectively augments presynaptic GABA release. Furthermore, the in vivo results demonstrate that this spinal action translates into significant relief of neuropathic pain symptoms. **Conclusion:** AVP selectively enhances presynaptic GABA release in the spinal dorsal horn via V1a receptors. This specific enhancement of GABAergic transmission represents a key cellular mechanism for AVP-mediated analgesia. These findings suggest that the spinal AVP-V1a receptor pathway may be a promising therapeutic target for neuropathic pain.

Disclosures: Y. Yamamoto: None. **M. Yamanaka:** None. **W. Taniguchi:** None. **N. Nishio:** None. **Y. Matsuyama:** None. **T. Ueno:** None. **R. Miyake:** None. **Y. Kaimochi:** None. **T. Nakatsuka:** None. **H. Yamada:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.03/Z10

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01 NS127428
T32 DK112751

Title: The role of spinal C5aR1 signaling in neuropathic pain following peripheral nerve injury

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Abstract: Chronic neuropathic pain affects approximately 10% of the population, and current pharmacological treatments provide satisfactory relief for only a minority of patients. Recent meta-analyses have identified pain-regulated genes, most notably including those involved in the complement system activation, in the regulation of chronic neuropathic pain. Among these complement products, C5a seems to be especially important in the development and maintenance of neuropathic pain, although the underlying cellular and molecular mechanisms are not fully understood. Using the Spared Nerve Injury (SNI) mouse model of neuropathic pain, we found that pharmacological inhibition of C5a/C5aR1 signaling by a potent and selective C5aR1

antagonist PMX205 significantly decreased mechanical allodynia. The analgesic effect of PMX205 administration was transient and could be observed with repeated administration for up to 8 weeks post-SNI. In contrast, deletion of C5aR1 produced a significant delay of approximately two weeks in the development of mechanical allodynia. To elucidate the molecular basis of this behavioral delay, we performed bulk RNA-sequencing of the spinal dorsal horn in wild-type (WT) and global C5aR1 knockout (KO) mice at Day 0, Day 7, and Day 28 post-SNI. Although KO mice are temporally delayed in the development of SNI-induced allodynia, they exhibited a substantially larger transcriptional response at Day 7 compared to wild-type mice (3,843 vs. 627 differentially expressed genes). Both genotypes upregulated canonical disease-associated microglia (DAM) markers (Trem2, Apoe, Mertk), indicating that microglial activation alone is insufficient to drive nociception in the absence of C5aR1 signaling. Critically, KO mice exhibited exclusive suppression of nociceptor genes (TrkA, NGFR, Tac1, P2RX3, Scn11a, GRIK1) and genes associated with synaptic plasticity (Fos, Egr1, CaMKII); pathway enrichment analysis confirmed KO-specific downregulation of nociception and synaptic plasticity. Together, these findings indicate that microglial C5aR1 signaling regulates the neuropathic pain development and shapes spinal cord transcriptional responses to nerve injury. These results identified C5aR1 as a key modulator of neuroimmune signaling underlying pain-related gene expression and behavioral hypersensitivity after peripheral nerve injury.

Disclosures: R. Som: None. **K.S. Solanki:** None. **A. Keyes:** None. **L. Shutov:** None. **G. Deng:** None. **A.G. Bassuk:** None. **Y.M. Usachev:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.04/Z11

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant NS101880
NIH grant NS132398
Pamela and Wayne Garrison Distinguished Chair Endowment

Title: LRRC8A limits spinal NMDA receptor activity and neuropathic pain independent of volume-regulated anion channel activity

Authors: *Y. HUANG[1], D. JIN[2], H. CHEN[1], S.-R. CHEN[2], H.-L. PAN[1];
[2]Anesthesiol., [1]The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Leucine-rich repeat-containing protein 8A (LRRC8A) constitutively limits synaptic expression and activity of N-methyl-D-aspartate receptors (NMDARs) in the spinal dorsal horn. However, because LRRC8A is the obligatory subunit of volume-regulated anion channels (VRACs), it remains unclear whether this action depends on VRAC function or on the LRRC8A protein itself. The N terminus of LRRC8A critically regulates VRAC pore properties and

channel gating. Here, we used an LRRC8A N-terminal mutant lacking VRAC activity to determine whether VRAC function contributes to NMDAR regulation. In *Lrrc8a*-deficient HEK293 cells, expression of wild-type LRRC8A restored VRAC currents, whereas a proline-to-cysteine substitution at position 3 (P3C mutant) abolished VRAC activity. Both wild-type LRRC8A and the P3C mutant similarly interacted with the GluN1 subunit of NMDARs, reduced NMDAR surface expression, and suppressed NMDAR currents in cells expressing GluN1/GluN2A receptors. In rats with spinal nerve ligation, intrathecal delivery of lentiviruses expressing either wild-type LRRC8A or the P3C mutant reversed tactile, pressure, and thermal hypersensitivity. Both constructs also attenuated injury-induced presynaptic and postsynaptic NMDAR hyperactivity in spinal dorsal horn neurons and reduced GluN1 levels in spinal synaptosomes. Furthermore, in mice lacking *Lrrc8a* in primary sensory neurons, intrathecal expression of either construct similarly alleviated pain hypersensitivity and reduced hyperactivity of NMDARs at primary afferent central terminals. However, only wild-type LRRC8A restored VRAC currents in dorsal root ganglion neurons. These findings demonstrate that LRRC8A suppresses NMDAR synaptic trafficking and activity in the spinal cord through a VRAC-independent mechanism, highlighting a potential therapeutic target for neuropathic pain without broadly disrupting VRAC function.

Disclosures: Y. Huang: None. **D. Jin:** None. **H. Chen:** None. **S. Chen:** None. **H. Pan:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.05/Z12

Topic: E.01. Somatosensation – Pain and Itch

Support: KAKENHI JP23K27330
KAKENHI JP24K22166
KAKENHI JP26K02326
Takeda Science Foundation
Uehara Memorial Foundation

Title: TRPC3 in spinal dorsal horn neurons facilitates neuropathic pain and PLC-induced mechanical hypersensitivity

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Abstract: Neuropathic pain is a debilitating chronic condition primarily caused by peripheral nerve injury; however, its cellular and molecular mechanisms remain poorly understood. Transient receptor potential canonical 3 (TRPC3), a TRP channel activated downstream of the Gq-phospholipase C (PLC) pathway, is expressed in the somatosensory system. Here, we

demonstrate the pathophysiological role of TRPC3 in the development of neuropathic pain using a partial sciatic nerve ligation (pSNL) mouse model and TRPC3-knockout mice. TRPC3 deficiency attenuated pain hypersensitivity in the pSNL model. TRPC3 is predominantly expressed in neurons of the spinal dorsal horn. Knockdown of TRPC3 in these neurons alleviated neuropathic pain, whereas its activation induced acute mechanical hypersensitivity. Furthermore, PLC-induced mechanical hypersensitivity, which is associated with neuropathic pain pathology, was suppressed in TRPC3-knockout mice. These findings elucidate TRPC3-mediated cellular and molecular mechanisms underlying neuropathic pain and suggest that TRPC3 may serve as a therapeutic target for its treatment.

Disclosures: K. Tamada: None. **S. Tobori:** None. **H. Shirakawa:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.06/Z13

Topic: E.01. Somatosensation – Pain and Itch

Support: PSC-CUNY Award # GR-00017928

Title: Bidirectional Nociceptive State Modulation by Capsaicin and Aprepitant in Mice Quantified Using Fiber Photometry Targeting NK1R+ Superficial Dorsal Horn Neurons

Authors: *M. MIAH[1], G. G. LI[2], G. CATALDO[1];
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Abstract: Neurokinin-1 receptor-expressing (NK1R+) projection neurons in laminae I-IIo of the superficial dorsal horn are a principal output relaying nociceptive signals and are implicated in central sensitization, yet their dynamics during evoked pain and acute sensitization are rarely quantified in vivo in behaving animals. To address this gap, we developed a novel surgical approach to implant a fiber optic intraspinally, providing access to the laminae. We performed neurophysiological recordings (fiber photometry) targeting the lumbar enlargement (L4/L5) to determine whether NK1R+ activity provides real-time stimulus-dependent readout of nociceptive state, increases with capsaicin-induced sensitization, and is reversed by NK1R+ inhibition. NK1R-CreER mice underwent intraspinal microinjection of a Cre-dependent adeno-associated virus encoding the calcium indicator jGCaMP8s into lumbar laminae I-IIo followed by spinal implantation of an optical fiber. Calcium-dependent fluorescence (ΔF/F) was recorded using 470 nm excitation with a 405 nm isosbestic control channel for motion and hemodynamic correction during graded von Frey stimulation and Hargreaves thermal pain assays. Each mouse was tested across three phases within a single recording session (baseline, intraplantar capsaicin, and the NK1R antagonist aprepitant), serving as their own controls. Capsaicin produced behavioral hyperalgesia and stimulus-evoked NK1R+ ΔF/F transients, with stimulus-dependent readout

across von Frey forces and during Hargreaves trials. Aprepitant, relative to capsaicin, produced behavioral antihyperalgesia and returned the evoked signal towards baseline in both assays. Across both conditions, evoked ΔF/F covaried with withdrawal probability on a trial-by-trial basis. Post hoc immunohistochemistry confirmed Cre-dependent expression in the superficial dorsal horn and verified fiber placement. These findings suggest that spinal photometry of NK1R+ activity can be used as a bidirectionally sensitive measure of nociceptive state, and provides an avenue to study acute and chronic pain in an interpretively agnostic and ethologically relevant manner in freely behaving animals.

Disclosures: M. Miah: None. **G.G. Li:** None. **G. Cataldo:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.07/Z14

Topic: E.01. Somatosensation – Pain and Itch

Support: 1R01DA055578-01
4R01AG065329 - 02
4R00AT012658-02
R01-AA029124

Title: Metabolic reallocation in spinal cord oligodendrocytes drives chronic pain in mice through neuronal Aβ42 production

Authors: Y. FOTIO[1], ***S. AL MASRI**[2], Z. SHI[2], J. LE[2], S. DAS[5], V. I. RUBTSOVA[3], A. MABOU TAGNE[6], C. JANG[7,8], V. SWARUP[4], D. PIOMELLI[9];
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Abstract: Recent evidence implicates a metabolic switch within afferent spinal circuits as a key driver of the transition from acute to chronic pain following tissue injury, yet the cellular substrates and functional consequences remain incompletely defined. Using a combination of pharmacological and genetic approaches, we show that peripheral injury reprograms metabolism in spinal cord oligodendrocytes, initiating a molecular cascade that drives chronic pain through release of the amyloid peptide $A\beta_{42}$. After peripheral injury, mouse spinal oligodendrocytes downregulate myelin protein synthesis and upregulate lipid biosynthesis but reroute lipids toward neuroplastic remodeling and away from myelin maintenance. This reallocation disrupts myelin integrity and axonal function, causing neuronal accumulation of amyloid precursor protein, enhanced BACE1 expression, and $A\beta_{42}$ release during a critical temporal window for the

transition to pain chronicity. Blocking $A\beta_{42}$ production or clearing $A\beta_{42}$ within this window prevents the emergence of persistent pain. Oligodendrocyte-specific deletion of N-acylethanolamine acid amidase—a key regulator of cell metabolism and pain—prevents injury-induced $A\beta_{42}$ release and chronic pain development. These findings uncover an unexpected mechanistic link between chronic pain and Alzheimer's-like neurodegeneration and identify the NAAA→$A\beta_{42}$ pathway as a target for disease-modifying intervention.

Disclosures: Y. Fotio: None. **S. Al Masri:** None. **A. Mabou Tagne:** None. **V. Swarup:** None. **D. Piomelli:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.08/Z15

Topic: E.01. Somatosensation – Pain and Itch

Support: NASU 0124U001556
NASU 0124U001557
NASU 0125U002426
NASU 0125U001465

Title: Adrenergic control of primary afferent transmission and sensory processing in spinal lamina X

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Abstract: Descending pathways exert powerful control over nociceptive processing in the spinal cord. An important component of this regulation is the adrenergic system, which brainstem projections descend through the dorsolateral funiculus (DLF). Lamina X integrates primary afferent and descending inputs and plays an important role in nociceptive, particularly visceral, sensory processing. However, the cellular and synaptic mechanisms underlying adrenergic regulation of lamina X networks remain poorly understood. The aim of this study was to investigate the effects of noradrenaline (NA) on sensory processing within spinal lamina X using an *ex vivo* hemisected spinal cord preparation with intact L4-L5 dorsal roots from juvenile Wistar rats (P11-P12). Application of NA (20 μM) markedly reduced dorsal root potentials (DRPs) evoked by selective activation of both A- and C-fiber primary afferents. These findings directly demonstrate adrenergic presynaptic regulation of primary afferent terminals.

Importantly, NA also substantially suppressed DRPs evoked by DLF stimulation, indicating the involvement of adrenergic modulation in descending control of primary afferents. At the level of individual lamina X neurons, NA exerted both presynaptic and postsynaptic effects. In approximately 60% of neurons, NA induced a small slow inward current (10-40 pA). Simultaneously, NA dramatically reduced dorsal-root-evoked excitatory synaptic responses, including both mono- and polysynaptic inputs arising from A- and C-fiber primary afferents. Notably, these effects were observed even in neurons lacking detectable NA-induced postsynaptic currents, further supporting a predominantly presynaptic mechanism. Adrenergic modulation was both synapse- and cell-specific: individual monosynaptic inputs converging onto the same neuron displayed markedly different sensitivities to NA, and the overall degree of suppression also varied between neurons, ranging from nearly complete block of primary afferent input to only minor effects. NA also reduced the number of action potentials generated by lamina X neurons in response to C-fiber stimulation, consistent with its antinociceptive action. In addition, inhibitory postsynaptic currents evoked by dorsal root stimulation were substantially suppressed, demonstrating that adrenergic regulation influences both excitatory and inhibitory components of lamina X networks. These findings identify adrenergic modulation of primary afferent transmission as an important mechanism underlying descending control of sensory processing in spinal lamina X.

Disclosures: I.O. Blashchak: None. **A.S. Andriievska:** None. **O.V. Halaidych:** None. **S.V. Romanenko:** None. **A.O. Nechai:** None. **B.V. Safronov:** None. **N.V. Voitenko:** None. **V.V. Krotov:** None. **P.V. Belan:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.09/Z16

Topic: E.01. Somatosensation – Pain and Itch

Support: FAPESP: 2022/04387-6
FAPESP: 2025/12821-6
FAPESP: 2023/13491-4

Title: Sex- and Condition-Specific Expression of Oxytocin Receptors in the Human Spinal Cord

Authors: *D. B. SOUZA[1], D. TAVARES FERREIRA[2], I. SANKARANARAYANAN[3], K. GABRIEL[4], L. HE[5], T. J. PRICE[6];
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Abstract: Research increasingly highlights the analgesic potential of neuropeptide oxytocin (OT) in both preclinical and clinical studies. A primary mechanism involves OT's direct action within laminae I and II of the spinal cord dorsal horn. Previous characterizations of spinal oxytocin receptors (OTRs) have largely relied on pharmacological tools in animal models or cell culture systems; thus, mapping these receptors in human tissue represents a critical methodological advancement with translational implications for chronic pain management. This study aimed to characterize OTR expressions within laminae I and II of the human spinal cord. Post-mortem spinal cord tissue from organ donors was obtained via the Southwest Transplant Alliance (STA), with all procedures approved by the Institutional Review Board at the University of Texas at Dallas (protocol Legacy-MR-15-237). We performed multiplexed RNAscope *in situ* hybridization to evaluate OTR transcripts and their cellular localization. Our results reveal distinct sex differences in OTR co-localization: males exhibited a significantly higher proportion of OTR expression in PVALB+ GABAergic neurons (t= -2,74, p = 0.0034) and astrocytes (t= -2,45, p = 0.0495) compared to females. No sex differences were observed in total co-localization with the neuronal marker NeuN. Furthermore, we detected a significant decrease in OTR expression in donors with a history of chronic pain (F(1,9) = 3,46, p = 0.0457), independent of biological sex. Taken together, these findings provide novel insights into the cellular distribution of OTRs in the human spinal cord and highlight sex-specific and pathological alterations that could guide targeted therapies for chronic pain.

Disclosures: D.B. Souza: None. **D. Tavares Ferreira:** None. **I. Sankaranarayanan:** None. **K. Gabriel:** None. **L. He:** None. **T.J. Price:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.10/Z17

Topic: E.01. Somatosensation – Pain and Itch

Support: Fapesp 2024/05877-2
Fapesp 2022/04387-6

Title: The Role of Spinal Cord Oxytocin Receptors in Hyperalgesic Priming model in mice.

Authors: *N. UREL-CARNEIRO, A. BRAGA DIAS, L. CANTO DE SOUZA, D. B. SOUZA; São Paulo state university- Sch. of Pharmaceut. Sci., Araraquara, Brazil

Abstract: Chronic pain conditions have a significantly higher prevalence in women and involve physical, psychological, and sociocultural aspects. Oxytocin, a neuropeptide involved in pain modulation and affective-emotional processes, has emerged as a potential target for the treatment of chronic pain. This study aims to determine whether hyperalgesic priming model induces changes in oxytocin receptor expression in laminae I and II of the spinal cord and whether oxytocin treatment can modulate these alterations in mice. In the hyperalgesic priming model, an

initial nociceptive stimulus, such as a plantar incision, is applied and animals are allowed to recover. Subsequently, a second stimulus, typically a local injection of prostaglandin E_2 (PGE_2), is administered to assess the development of persistent pain sensitization. Male and female Swiss-Webster mice (postnatal day 60) were assigned to experimental groups according to sex and treatment. Oxytocin was administered intraperitoneally at doses of 1 or 5 mg/kg. Oxytocin receptor expression was evaluated by immunofluorescence in spinal cord laminae I and II. Fluorescence images were acquired and quantified by measuring mean fluorescence intensity using ImageJ. Student's *t*-test revealed a significant reduction in oxytocin receptor expression in saline-treated animals subjected to hyperalgesic priming compared with non-primed animals, both in males ($t(4) = -4.21$, $p = 0.01$) and females ($t(4) = -3.23$, $p = 0.03$). One-way ANOVA showed no significant effect of oxytocin treatment on receptor expression in either sex. These findings indicate that hyperalgesic priming reduces oxytocin receptor expression in the spinal cord. However, oxytocin treatment at the doses tested did not reverse or prevent these changes. The reduction in receptor expression observed after hyperalgesic priming suggests that alterations in the spinal oxytocinergic system may contribute to pain-related neuroplasticity associated with chronic pain development.

Disclosures: N. Urel-Carneiro: None. **A. Braga Dias:** None. **L. Canto De Souza:** None. **D.B. Souza:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.11/Z18

Topic: E.01. Somatosensation – Pain and Itch

Support: PAPIIT-UNAM, Grant Agreement No. IN227225
CONACyT Mexico, Grant Agreement No. A1-S-23631

Title: Pharmacological and molecular basis of the spinal sexual dimorphism involved in the oxytocin-induced inhibition of nociception elicited by lipopolysaccharide

Authors: *A. GONZÁLEZ-HERNÁNDEZ, G. MARTINEZ-LORENZANA, A. ESPINOSA DE LOS MONTEROS ZÚÑIGA, M. CONDES-LARA;
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Abstract: Intrathecal LPS injection at the spinal cord level induces neuroinflammation, leading to hypersensitivity to tactile stimuli, an effect attributed to the release of proinflammatory mediators by glial cells. Activation of oxytocin receptors (OTRs) in the spinal cord induces antinociception via a biased signalling mechanism (1,2). The effects of oxytocin and biased oxytocin receptor agonists, such as carbetocin or atosiban, on LPS-induced sensitisation were analysed at the spinal level in male and female rats. Dose-response curves for LPS and oxytocin were developed for both sexes. Carbetocin and atosiban were employed to elucidate the potential

intracellular mechanisms triggered by OTR activation. The drugs were administered 15 min after LPS injection. Nocifensive behaviour (i.e., paw withdrawal threshold, PWT) induced by LPS was analysed using von Frey filaments over six hours following LPS administration. LPS increased sensitivity to tactile stimuli in a dose-dependent manner, with females (0.02 ng; ED_{75}) being more sensitive than males (3.3 ng; ED_{75}). Electrophysiological data from the spinal cord showed that the neural activity of second-order wide-dynamic-range (WDR) cells was preferentially enhanced in female rats compared with male rats. Moreover, while oxytocin administration decreased LPS-induced nociception in a dose-dependent manner, females were less sensitive to oxytocin (10 nmol) than males (1 nmol); in both cases, the effect was reversed by L-368,899 (an OTR antagonist). The sexual dimorphism in behavioural nociception observed with LPS and oxytocin was abolished in females pretreated with an antagonist to oestrogen receptors ($ER_{\alpha/\beta}$). Although atosiban (1 nmol; biased OTR-Gi ligand) inhibited LPS-induced nociception in both sexes, carbetocin (1 nmol; biased OTR-Gq ligand) had no effect. Atosiban-induced antinociception was prevented by intrathecal pretreatment with pertussis toxin (an inhibitor of the Gi pathway). Moreover, at the spinal cord level, atosiban treatment reduced LPS-induced activation of GFAP and Iba-1 cells. In addition to the sexual dimorphic effects, these data suggest that OTR activation attenuates LPS-induced hypersensitivity via the OTR-Gi pathway. (1) *Neuropharmacology* 2025;275:110487. (2) Curr Top *Behav Neurosci 2017:35:3-29.*

Disclosures: A. González-Hernández: None. **G. Martinez-Lorenzana:** None. **A. Espinosa de los Monteros Zúñiga:** None. **M. Condes-lara:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.12/Z19

Topic: E.01. Somatosensation – Pain and Itch

Support: NASU grant 0124U001557
NASU grant 0125U001123
NASU grant 0124U001556
NASU grant 0125U002426
NASU grant 0125U001465

Title: Complete Freund's Adjuvant (CFA)-induced peripheral inflammation differentially alters afferent-driven synaptic input to spinal lamina I neurons

Authors: S. V. ROMANENKO[1], V. KROTOV[2], B. V. SAFRONOV[3], ***N. V. VOITENKO**[4,5], P. V. BELAN[1];
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Abstract: Chronic pain is a debilitating condition caused by propound changes in the functioning of peripheral and central nervous system including the superficial dorsal horn of the spinal cord, responsible for primary processing of nociceptive information. Over the last two decades, pain-induced cellular and molecular changes have been fairly well documented for spinal laminae II and III. Yet, the alterations occurring in lamina I cells remain largely unknown. In the present study, we combined patch clamp recordings in intact ex-vivo spinal cord with saturating electrical stimulation (+150 μA /1 ms) of spared L4 and L5 dorsal roots (DRs) to study how peripheral inflammation, induced by Complete Freund's Adjuvant (CFA) subcutaneous injection into the hind paw of adult mice, affects L4 spinal lamina I neurons. With over 200 cells analyzed, we may report the following. In physiological conditions, the majority of L4 neurons received excitatory polysynaptic A- and C-fiber-driven input from both L5 and L4 DRs, though L5-driven input was typically more robust. At the same time, monosynaptic input indicating direct synaptic connections between primary afferents and spinal neurons was not so abundant: the incidence of L5-driven monosynaptic input from Aβ-, Aδ- and C-fibers did not exceed 30%, 50% and 15%, respectively; for L4-driven monosynaptic input, these numbers were even lower. Meanwhile, peripheral inflammation differentially altered synaptic input to lamina I neurons. Median integral of synaptic current was significantly increased for L5-driven input but remained roughly the same for L4-driven one. CFA-treated animals generally showed higher incidence of monosynaptic input but we were unable to validate this statistically. Median amplitudes of monosynaptic input were augmented for both L4 and L5 dorsal roots but this effect reached significance only for Aβ-fiber-driven input. Surprisingly, increased L5-driven synaptic input did not influence evoked spike generation: cell-attached recordings revealed that CFA injections did not alter the pattern of spiking in response to saturating DR stimulation. Given that we failed to find any meaningful changes of membrane excitability, we may conclude that lamina I neurons possess a compensatory mechanism that prevents them from excessive action potential firing thus protecting them from excitotoxicity despite substantial increase in synaptic input.

Disclosures: S.V. Romanenko: None. **V. Krotov:** None. **B.V. Safronov:** None. **N.V. Voitenko:** None. **P.V. Belan:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.13/Z20

Topic: E.01. Somatosensation – Pain and Itch

Support: T32 Grant 5T32NS126120-03
DoD Grant SC210118P1
NIH Grant 1R01 NS111234

Title: Neural geometry of spinal sensory encoding in chronic spinal cord injury

Authors: *A. R. TWYMAN[1], G. N. MORENO ROMERO[1], J. LUCAS-ROMERO[2], L. LOPEZ-NIETO[2], J. G. MCPHERSON[1,2,3];
[1]Biomed. Engin., Washington Univ. in St. Louis, St. Louis, MO; [2]Physical Therapy, [3]Anesthesiol., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Chronic spinal cord injury (SCI) causes spinal networks below the level of injury to reorganize, often leading to SCI-related neuropathic pain (SCI-NP). Some clinical features of SCI-NP have a relatively intuitive neural underpinning, such as hyperalgesia and an increased responsiveness of spinal wide dynamic range and nociceptive-specific neurons to nociceptive sensory feedback. More enigmatic features of SCI-NP, such as allodynia and spontaneous pain, are less directly linked to changes in spinal neuron excitability. These features of SCI-NP may instead be represented by changes in the structure of neural population-level patterns of sensory transmission, which requires a different analytical framework and tools. Neural manifold analysis has emerged as a powerful approach to characterizing the population-level dynamics underlying complex sensorimotor and cognitive processes in brain networks. Although manifold analysis also holds considerable promise for characterizing spinal networks, this application is largely unexplored - particularly for sensory transmission. This study utilized a neural manifold framework to characterize spinal population-level sensory encoding, how it is altered by chronic SCI, and to determine whether and how clinical features of SCI-NP manifest at the manifold level. All studies were conducted *in vivo* in adult male Sprague Dawley rats, and all procedures were approved by the IACUC of Washington University in St. Louis. Microelectrode arrays were implanted into the lumbar enlargement of neurologically intact rats, those with chronic SCI-NP, and those with chronic SCI that lacked SCI-NP. Broadband intraspinal neural activity was recorded both during periods of innocuous and noxious cutaneous stimulation of the periphery and during quiescence. Single-unit activity was discriminated offline, and neurons were functionally classified according to their stimulus response. We then used PCA to transform the high-dimensional population activity into low-dimensional neural manifolds. In neurologically intact rats, population-level representations of nociceptive and non-nociceptive activity could be distinguished by spatiotemporal features of their respective manifolds. In rats with SCI, however, including those with SCI-NP, these distinctions became less apparent, suggesting a conflation of nociceptive and non-nociceptive encoding. These findings establish a framework for examining spinal sensory processing at the population level and provide insights into the mechanisms underlying SCI-NP.

Disclosures: A.R. Twyman: None. **G.N. Moreno Romero:** None. **J. Lucas-Romero:** None. **L. Lopez-Nieto:** None. **J.G. McPherson:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.14/Z21

Topic: E.01. Somatosensation – Pain and Itch

Support: UTSW Endoward Scholor Program
Rita Allan Foundation

Title: Therapeutic Targeting of the Spinal Cord Output Neurons for Pain Control

Authors: *V. DUBEY;
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Abstract: Therapeutic Targeting of the Spinal Cord Output Neurons for Pain Control
Vivek Dubey[1], Satoshi Ishishita[1], Allan-Hermann Pool[1, 2]1. Department of Neuroscience, O'Donnell Brain Institute, University of Texas Southwestern Medical Center2. Department of Anesthesia and Pain Management, University of Texas Southwestern Medical CenterChronic pain including lower back, musculoskeletal, and cancer associated pain often requires lifelong treatment with abuse-prone analgesics, leaving approximately 8.5% of U.S. adults with persistent high-impact pain. Therefore, there is an urgent need for durable, non-addictive therapeutic strategies for pain. Spinal projection neurons (SPNs), which transmit nociceptive signals from the spinal cord to the brain, represent a promising but underexplored target for precision pain management. However, the specific SPN subclasses that mediate distinct pain modalities, and their therapeutic targeting remain poorly defined. In preliminary work, we have identified 12 transcriptionally distinct pain activated SPN classes that link the lumbar spinal cord to the brain, each defined by unique cell-surface receptors that are selectively enriched in specific SPN populations and absent or under-represented in the >100 other lumbar spinal cord neuron types. Here, we tested the feasibility of SPN level pain interventions by targeted lesioning of five of the 12 spinal projection neurons with Tacr3 targeting ligand-drug conjugate Neurokinin B-Saporin (NKB-SAP). The Focal delivery of NKB-SAP to the lumbar spinal cord produced profound and sustained attenuation of noxious heat- and mechanical stimulus-evoked pain behaviors, as assessed by hot plate, Hargreaves, and von Frey assays. Critically, Tacr3+ SPN ablation also abolished mechanical hypersensitivity in a model of chronic neuropathic pain, demonstrating efficacy across both acute nociceptive and chronic pathological pain states while leaving locomotion intact. Furthermore, we characterize new targets for targeted lesioning of pain mediating SPN classes for a combinatorial and once-and-done strategy for chronic pain management. Together, these findings demonstrate the feasibility of SPN subclass-specific immunotoxin strategies for precise and durable pain relief and advance non-addictive precision therapeutics for chronic pain.

Disclosures: V. Dubey: None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.15/Z22

Topic: E.01. Somatosensation – Pain and Itch

Support: UTSW Endowed Scholars Program (A.-H.P.)
JSPS Overseas Research Fellowships (S.I.)
Rita Allen Foundation (A.-H.P.)
McKnight Neurobiology of Brain Disorders Award (A.-H.P.)

Title: Cell-type-resolved functional mapping of spinal projection neurons across pain states

Authors: *S. ISHISHITA[1], L. CANO GOMEZ[1], A.-H. POOL[1,2,3];
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Abstract: Spinal projection neurons (SPNs) transmit nociceptive and somatosensory information from the spinal cord to supraspinal centers that regulate pain-related behavior. Although SPNs are essential for central pain perception, their cellular diversity, projection patterns, stimulus-evoked activity, and causal contributions to pain-related behavior have remained poorly understood. To address this gap, we combined single-cell and spatial transcriptomics, retrograde viral tracing, immediate-early-gene-based activity mapping, and neural circuit dissection to define the organization and activity patterns of ascending spinal output pathways. We used spatial transcriptomics together with cell-type-resolved retrograde tracing from supraspinal structures implicated in pain processing to identify 18 transcriptomically distinct SPN types. These SPN types showed partially overlapping but distinct spatial distributions. Projection mapping revealed diverse projection patterns among individual SPN types, with some classes showing similar projection profiles. To link this diversity to function, we used immediate-early-gene-based stimulus-to-cell-type mapping to examine how distinct pain-related conditions, including surface and deep tissue insults, as well as non-pain somatosensory stimuli, engage specific SPN types. These studies revealed that SPN types are differentially but not exclusively recruited across stimuli, with each condition engaging a distinct activity pattern across SPN types. These findings suggest that SPN types are differentially tuned to distinct somatosensory stimuli and may contribute to pain-related behaviors. This work also identified pain-engaged SPN populations based on spatial localization, projection patterns, and stimulus-evoked activity. Notably, noxious stimulus-engaged SPN populations were enriched in lamina I and the lateral spinal nucleus. To test the causal roles of SPN types in pain-related behaviors, we established genetic tools to target and manipulate individual SPN types and defined subtype combinations. In parallel, we implemented quantitative behavioral readouts using the Blackbox high-speed video recording system, including measurements of nocifensive behaviors and changes in dynamic weight bearing. Together, these studies establish cellular principles by which ascending spinal output pathways contribute to pain-related behavior.

Disclosures: S. Ishishita: None. **L. Cano Gomez:** None. **A. Pool:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.16/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Support: Research partially funded by the project IPN [SIP 20250356 and 20251146 IPN]. SECIHTI for the postdoctoral fellowship, CVU 487025.

Title: Biochemical Characterization of Cerebrospinal Fluid Associated with Copulatory Analgesia in Male Rats Using FTIR-ATR Spectroscopy

Authors: *C. E. AGUILAR-PÉREZ[1], R. DOMÍNGUEZ ORDÓÑEZ[4], J. L. ENCARNACIÓN SÁNCHEZ[5], V. LOPEZ GAYOU[2], O. GONZALEZ-FLORES[6], R. DELGADO MACUIL[3]; [1]Inst. Politécnico Nacional (IPN), Tlaxcala, Mexico; [2]Inst. Politécnico Nacional (IPN), Puebla, Mexico; [3]Inst. Politécnico Nacional (IPN), Tepetitla de lardizabal, Mexico; [4]Benemérita Univ. Autónoma de Puebla, Chiautempan, Mexico; [5]Autonomous Univ. of Tlaxcala, Tlaxcala, Mexico; [6]CINVESTAV-UAT, Ixtacuixtla, Mexico

Abstract: Copulatory analgesia is a physiological response characterized by a transient reduction in pain sensitivity during and after sexual behavior, associated with the activation of endogenous neurochemical systems. Cerebrospinal fluid (CSF) represents a biological matrix of particular interest for investigating these changes, as it reflects biochemical modifications occurring within the central nervous system. The aim of this study was to evaluate potential molecular changes in the CSF of male rats during different phases of copulatory behavior using Fourier-transform infrared spectroscopy with attenuated total reflectance (FTIR-ATR). CSF samples were collected from a control group (CTL, n = 7), during the first ejaculatory series (EJS1, n = 9), after the first ejaculatory series (PE1, n = 10), during the second ejaculatory series (EJS2, n = 13), and after the second ejaculatory series (PE2, n = 9). FTIR-ATR spectra were analyzed by principal component analysis (PCA) in the spectral regions 1024-1180 cm^{-1} (carbohydrates), 1500-1698 cm^{-1} (amide I and II bands), and 2850-3000 cm^{-1} (C-H vibrations mainly associated with lipids). Preliminary results revealed substantial overlap among experimental groups across all three spectral regions. In the carbohydrate region, PC1 and PC2 explained 70.0% of the total variance, whereas in the amide and lipid regions they accounted for 99.3% and 99.1% of the variance, respectively. Although no clear group separation was observed, distinct dispersion patterns suggest the presence of biochemical variations associated with different phases of copulatory behavior. Further studies with larger sample sizes and complementary analyses are needed to confirm these findings.

Disclosures: C.E. Aguilar-Pérez: None. **R. Domínguez Ordóñez:** None. **J.L. Encarnación Sánchez:** None. **V. Lopez Gayou:** None. **O. Gonzalez-Flores:** None. **R. Delgado Macuil:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.17/Z23

Topic: E.01. Somatosensation – Pain and Itch

Support: CIHR PJT-162404

Title: Redistribution of primary afferent drive onto spinal parvalbumin neurons after nerve injury

Authors: *H. QIU[1], H. WILDNER[3], H. U. ZEILHOFER[4], R. DALLEL[5], C. PEIRS[6], R. SHARIF NAEINI[2];
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Abstract: The dorsal horn of the spinal cord contains highly organized circuits that process somatosensory information, including touch and pain. Interneurons play a key role in segregating these inputs, and loss of inhibition is a hallmark of neuropathic pain, leading to mechanical allodynia, where innocuous touch is perceived as painful. Disinhibition can be attributed to a decrease in the synapses of inhibitory neurons onto their targets, a decrease in the intrinsic excitability of these inhibitory neurons, or a decrease in their recruitment by primary afferents. Here, we examine the third scenario and examined the activation of inhibitory parvalbumin-expressing neurons (PVNs) by Aβ low-threshold mechanoreceptors (Aβ-LTMRs). Our work reveals an additional level of complexity, where Aβ-LTMRs activate both inhibitory and excitatory PVNs. Under naive conditions, Aβ input preferentially recruits inhibitory PVNs (iPVNs), whereas excitatory PVNs (ePVNs) receive feedforward inhibition. Following peripheral nerve injury, Aβ afferent connectivity, synapse density, and spontaneous synaptic events remained largely preserved, yet circuit recruitment was reorganized. Aβ-driven activation of iPVNs exhibited increased failure rates and degraded temporal precision, while ePVNs showed increased excitatory drive. Bidirectional chemogenetic manipulation revealed opposing contributions of these populations to mechanical sensitivity *in vivo*, with iPVNs suppressing and ePVNs promoting mechanical hypersensitivity. Further, we identify a previously uncharacterized population of inhibitory interneurons as candidate mediators of Aβ-driven feedforward inhibition onto ePVNs. Together, these findings reveal that neuropathic pain emerges from a redistribution of primary afferent drive away from inhibitory and toward excitatory spinal pathways. Our results establish dynamic circuit reallocation of primary afferent inputs as a mechanism of spinal touch gating and positions it as a key determinant of mechanical allodynia.

Disclosures: H. Qiu: None. **H. Wildner:** None. **H.U. Zeilhofer:** None. **R. Dallel:** None. **C. Peirs:** None. **R. Sharif Naeini:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.18/Z24

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH/NINDS contract 75N95024D00038

Title: Assessment of Duloxetine Efficacy in the Rat Spinal Nerve Ligation (SNL) Model on Wide Dynamic Range (WDR) Neuron Activity Using In vivo Electrophysiology

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Abstract: In the development of novel pain therapeutics, recording the activity of WDR neurons in the dorsal horn provides a powerful approach to evaluate the effects of analgesics on pain-induced hyperexcitability. In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), PsychoGenics characterized the effects of duloxetine, a clinically used analgesic, on WDR neuronal activity in the L5/L6 spinal nerve ligation (SNL) model of neuropathic pain in male and female Sprague Dawley rats (assay adapted from Zhao et al., DOI: 10.1002/0471141755.ph1115s66). The SNL model was established by tight ligation of the L5 and L6 spinal nerves. Fourteen days after surgery, rats with consistent ipsilateral paw withdrawal thresholds of ≤3.0 g in response to von Frey stimulation were selected for testing. Under urethane anesthesia, the L4-L6 spinal segments (lumbar enlargement) were exposed via laminectomy for WDR neuron recordings. Duloxetine (3, 10, 30 and 60 mg/kg, PO), a serotonin norepinephrine uptake inhibitor, significantly reduced spontaneous WDR neuronal activity compared to vehicle, except the 3 mg/kg that did not show efficacy in female rats. Brush-evoked responses were significantly decreased at all doses tested compared to vehicle. Duloxetine also markedly attenuated von Frey-evoked responses across the full range of mechanical stimuli (2, 4, 8, 15, 26, and 60 g), with the 3 mg/kg dose showing limited but non-significant effect. Pharmacokinetic analysis demonstrated a positive relationship between plasma and brain exposure levels and the decrease in von Frey-evoked WDR neuron responses. Duloxetine showed a lower minimum effective dose on WDR neuronal activity with clear efficacy at 10 mg/kg (plasma exposure ≈ 0.1-0.2 μM and brain exposure at 0.3-0.8 μM) compared to 30 mg/kg on paw withdrawal threshold behavior. In summary, this assay provides a direct, quantitative measure of neuronal activity that is independent of behavioral confounds such as sedation or altered locomotion and therefore can be used as a complementary and informative method for assessing pain mechanisms underlying the pharmacological efficacy of analgesic agents.

Disclosures: S. Zhong: A. Employment/Salary (full or part-time):; PsychoGenics Inc. **D.P. Budac:** None. **D. Bleakman:** None. **M.A. Varney:** None. **S.A. Woller:** A. Employment/Salary (full or part-time):; NIH/NINDS. **C. Conrad:** A. Employment/Salary (full or part-time):; NIH/NINDS. **S. Iyengar:** A. Employment/Salary (full or part-time):; NIH/NINDS. **T. Hanania:** A. Employment/Salary (full or part-time):; PsychoGenics Inc. **A. Ghavami:** A. Employment/Salary (full or part-time):; PsychoGenics Inc.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.19/AA1

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant U19NS130608
NIH grant R01NS116694
NIH grant R01NS139492
CDMRP award HT9425-24-1-1006

Title: Human organotypic nervous tissue explants enable compartment-specific neuropeptide release and pharmacological interrogation

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Abstract: Translational pain research is limited by the scarcity of human tissue-based models that enable functional evaluation of nociceptive signaling and pharmacological responses. We developed a donor-derived human organotypic dorsal root ganglion (DRG)-spinal cord primary afferent architecture and directional signaling and spinal cord slice model. Neuropeptide release was quantified using calcitonin gene-related peptide (CGRP) and substance P ELISA, supported by immunohistochemistry. Functional activation was evoked using capsaicin applied to either DRG compartment or directly on spinal cord slice. Pharmacological modulation was assessed using morphine and bupivacaine, applied in compartment-specific paradigms. Tissue viability was evaluated using metabolic assays (MTS). In isolated human spinal cord explants, capsaicin evoked concentration-dependent CGRP and substance P release without affecting viability, establishing a functional assay of central nociceptive signaling. Additionally, neurokinin 1 receptor internalization was observed in response to capsaicin stimulation, showing post synaptic functional activity. In preserved DRG-spinal cord circuits, DRG stimulation produced CGRP release exclusively in the spinal cord, demonstrating functioning axons and compartmentalized neuropeptide release at central terminals. Pharmacological studies confirmed assay sensitivity, with morphine and general sodium channel blockade with bupivacaine reducing evoked CGRP release in spinal cord preparations. In the preserved circuit, inhibition of sodium channel-dependent signaling at the DRG abolished spinal CGRP release. Immunohistochemistry confirmed capsaicin-evoked CGRP signal in spinal terminals and its suppression by morphine and bupivacaine. We establish a human organotypic nociceptive circuit that preserves directional signaling and enables compartment-specific pharmacological interrogation of neuropeptide release. These preparations provide a translational system for evaluating analgesic mechanisms in human tissue and supports drug discovery.

Disclosures: S. Palomino: None. **K. Gabriel:** None. **T.J. Price:** None. **A.M. Patwardhan:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.20/AA2

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS111234
NIH Grant R01NS111234-04S1
NIH Grant R01NS111234-04S2

Title: Spatiotemporal organization of intraspinal local field potentials in awake, behaving mice

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Abstract: Local field potentials (LFPs) provide a population-level measure of neuronal network activity and are widely used to characterize communication within and between supraspinal networks. In contrast, little is known about the physiological properties of intraspinal LFPs, largely due to the difficulty of obtaining stable recordings from spinal circuits during natural behavior. The purpose of this study is to delineate normative features of intraspinal LFPs in awake, behaving mice - an essential pre-requisite for understanding how spinal encoding is altered following injury.All procedures were approved by the WUSTL IACUC. Adult male C57BL/6 mice had ultraflexible microelectrode arrays implanted into their lumbar enlargement. The arrays spanned the dorsoventral extent of the spinal gray matter, enabling simultaneous recordings from sensory- to motor-dominant spinal regions. Extracellular recordings were acquired during sensory behavioral testing (Von Frey, Dry Ice, and Hargreaves test) and spontaneous behavior in awake, freely moving animals. Broadband neural activity was processed to extract local field potentials for spectral analyses.As an initial exploratory study, we sought to characterize the spectral features of intraspinal LFPs during natural behavior and compare them with recordings obtained under anesthesia. To quantify sensory-related modulation of intraspinal LFPs, we measured the area under the power spectral density curve across spinal regions and frequency bands. Mechanical stimulation of the periphery increased LFP power relative to spontaneous activity in both awake and anesthetized animals. However, comparisons between awake and anesthetized recordings revealed state-dependent differences in spectral organization. Awake recordings exhibited greater low-frequency (theta-beta) power within the superficial dorsal horn and increased beta-to-high-gamma activity throughout deeper spinal regions. In contrast, anesthetized preparations demonstrated stronger beta-band activity within the deep dorsal horn and intermediate zone, while high-gamma power remained most prominent within

the intermediate zone. Together, these findings suggest that behavioral state substantially influences the spectral representation of sensory information within spinal networks.These studies provide one of the first characterizations of intraspinal LFPs in awake, freely behaving animals and establish a framework for future investigations of spinal network dynamics, sensorimotor integration, and circuit reorganization following spinal cord injury.

Disclosures: G.N. Moreno Romero: None. **A.R. Twyman:** None. **J.G. McPherson:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.21/AA3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01 NS096705
NIH Grant RM1 NS128775
NIH Grant R01 AR063772

Title: Effects of Dorsal Root Ganglia Stimulation on Somatosensory Processing in Healthy and Nerve-Injured Mice

Authors: *C. T. POTTER[1], C. WARWICK[1], H. J. STRATTON[1], H. KOERBER[1], S. ROSS[2]; [1]Neurobio., [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: To examine how Dorsal Root Ganglia Stimulation (DRGS) changes cell-type specific somatosensory activity in the dorsal root ganglia (DRG) and dorsal horn (DH), we have developed a novel experimental preparation to record the activity of defined populations in parallel. Through pan-neuronal expression of the Ca^{2+} sensor GCaMP, we record the activity of DRG neurons with a miniaturized fiberscope while simultaneously imaging activity in DH neurons with 2-photon microscopy. To resolve neural subpopulations, we express a nuclear mCherry in GAD2-expressing cells to distinguish between excitatory and inhibitory neurons, inject DiI into the parabrachial nucleus to label projection neurons, and classify neurons based on their response to a pharmacological profile of ligands. We refer to this combination of techniques as GRASP (Genetically-Resolved, Anatomically-Defined, Subpopulation Profiling). We demonstrate general suppression of both excitatory and inhibitory DH activity without substantial changes in DRG activity under DRGS. However, our neuron classification method revealed subpopulations of inhibitory interneurons that are enhanced by DRGS. We additionally report spontaneous activity in the DRG in mice with spared nerve injury (SNI) that is correlated with subpopulations of DH neurons, which is altered by DRGS.

Disclosures: C.T. Potter: None. **C. Warwick:** None. **H.J. Stratton:** None. **H. Koerber:** None. **S. Ross:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.22/AA4

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01DA047157
VA 1I01BX005114

Title: Signal pathway of bromodomain-containing protein to transcriptional factor cMyc plays a role in neuropathic pain induced by HIV glycoprotein 120 with morphine

Authors: X. TONG[1], M. PARDO[1], H. YI[1], S. LIU[1], J. GU[1], X. ZHU[1], J. K. LEE[2], R. LEVITT[1], ***S. HAO**[1,3];
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Abstract: Both the opioid and HIV epidemics are significant public health and social crises. People living with HIV have an increased prevalence of conditions associated with opioid analgesic misuse. HIV-infected opioid abusers show more severe neuropathology. Chronic pain is one of the most prevalent neurological complications in PLWH, persisting even in those who have achieved viral suppression through combination antiretroviral therapy. The exact molecular mechanisms of chronic pain experienced by HIV patients with opioid abuse are poorly understood, for which no effective treatment currently exists. Bromodomain-containing protein 4 (Brd4) is an epigenetic 'reader' that binds acetylated lysines in histones in brain neurons to mediate the transcriptional regulation. Transcription factor cMyc plays a crucial role in regulating various cellular processes, including cell cycle, proliferation, and metabolism, etc. Here, we established a neuropathic pain model of interaction of intrathecal HIV envelope glycoprotein 120 (gp120) and chronic morphine use in rodents. The combination of gp120 and morphine (gp120/M) induced persistent mechanical allodynia and thermal hyperalgesia. Application of gp120/M increased expression of spinal Brd4 and cMyc; immunostaining results showed that both Brd4 and cMyc were located in spinal dorsal horn neurons. Bioinformatic analysis predicted that there is one potential Brd4 binding site on the promoter region of cMyc in rodents/human. In gp120/M mice model, we examined effects of knockout of neuron-selective Brd4 **using** ARC^{CreERT2}::**Brd4$^{fl/fl}$ or cMyc in** ARC^{CreERT2}::**cMyc$^{fl/fl}$ cKO mice.** ARC^{CreERT2}::**Brd4$^{fl/fl}$ and** ARC^{CreERT2}::**cMyc$^{fl/fl}$ cKO mice** were injected with tamoxifen (Tam) or vehicle (corn oil) for 5 day. Tamoxifen treatment significantly reduced mechanical allodynia and thermal hyperalgesia for 3 weeks, suggesting that conditional knockout of neuronal Brd4 or cMyc reduces neuropathic pain. Western blots showed that there was significant increase in spinal Brd4 in oil-gp120/M group compared to oil-sham group, and there was significant decrease in Brd4 in Tam-gp120/M group compared to oil-gp120/M group. Similarly, there was significant increase in spinal cMyc in oil-gp120/M group compared to oil-sham group, and there was significant decrease in cMyc in Tam-gp120/M group compared to oil-gp120/M group. Interestingly, we found that knockout of Brd4 also reduced cMyc expression in the spinal cord.

Our results suggested that signal pathway of epigenetic 'reader Brd4 mediating cMyc expression plays an important role in gp120/M neuropathic pain model.

Disclosures: X. Tong: None. **M. Pardo:** None. **H. Yi:** None. **S. Liu:** None. **J. Gu:** None. **X. Zhu:** None. **J.K. Lee:** None. **R. Levitt:** None. **S. Hao:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.23/AA5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS111234
DoD Grant W81XWH2211100

Title: The impact of deep, surgical-plane anesthesia on intrinsic brainstem-derived modulation of spinal nociceptive transmission - implications for in vivo electrophysiological studies

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Abstract: The sensitivity of spinal nociceptive networks to peripheral sensory inputs is tightly regulated by neuromodulatory networks originating in the brainstem. Central to this control is an ascending-descending feedback loop in which ascending spinal projection neurons recruit descending brainstem neurons that in turn regulate segmental nociceptive transmission. It is well established that consciousness, diurnal cycles, physiological stressors, and numerous other factors govern the nature and extent to which these descending controls shape spinal nociceptive transmission. Surprisingly, however, it remains incompletely understood if/how descending nociceptive controls are shaped by anesthesia-induced unconsciousness, despite the ubiquity of pain-related studies using deeply anesthetized preparations.
To address this question, we characterized nociceptive sensory-evoked intraspinal neural activity in vivo in anesthetized rats both before and after complete interruption of descending supraspinal input. All procedures were approved by the WUSTL IACUC. Adult male Sprague-Dawley rats (n=5) were deeply anesthetized with urethane, and microelectrode arrays capable of simultaneously recording from the dorso-ventral extent of the spinal gray matter were implanted into the lumbar enlargement. Neural activity was recorded while inducing natural noxious and innocuous cutaneous feedback from the periphery, as well as during periods in which overt sensory feedback was absent (i.e., spontaneous activity). Data acquisition spanned both before and following a complete spinal transection at T8.
Our primary outcome measures were derived from multi-unit spiking activity and intraspinal local field potentials (LFPs). Multi-unit outcomes focused on changes in sensory-evoked

discharge rate the spatial extent of activation, while LFP-based outcomes focused on changes in spectral power and density. We found that multi-unit responsiveness to nociceptive sensory inputs was greater after transection than before. Acute transection also produced region-specific spectral reorganization of LFPs. Theta power increased throughout the spinal cord, alpha power increased in the superficial dorsal horn, and beta power increased in the deep dorsal horn and intermediate zone, while gamma power decreased in the dorsal horn, was unchanged in the intermediate zone, and decreased in the ventral horn. Together, these findings are consistent with the presence of a tonic descending inhibition and/or the preservation of ascending/descending feedback controls even under anesthesia.

Disclosures: G.N. Moreno Romero: None. **A.R. Twyman:** None. **J.G. McPherson:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.24/AA6

Topic: E.01. Somatosensation – Pain and Itch

Support: NS127428

Title: Single-bouton presynaptic gating revealed in ex vivo dual-color two-photon calcium imaging

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Abstract: Chronic pain affects approximately 100 million Americans and only a minority of patients experience satisfactory relief of their pain with currently available pharmaceutics. One type of chronic pain caused by direct injury to the nerve is called neuropathic pain, affecting ~10% of the overall population. Despite the prevalence, the underlying mechanisms of neuropathic pain are not well-defined, and better understanding of the mechanisms could lead to better treatment of this condition. Among various mechanisms, central sensitization, or the enhancement of synaptic transmission in the spinal cord, is thought to be especially important in the pathogenesis of neuropathic pain. Primary afferents, responsible for transducing painful stimuli, terminate in the spinal cord at the first sensory synapse. This synapse is a key regulator of pain signaling, and aberrant processes at this synapse can lead to an amplification of pain. As most studies have only examined the post-synaptic signaling of this synapse via patch-clamp recordings, the critical questions regarding the role of presynaptic changes in Ca^{2+} signaling in central sensitization have not been addressed. We have developed a method to examine Ca^{2+}

signaling in the spinal cord with high spatial (~0.5 μm) and temporal (~100 ms) resolution using an ex vivo intact spinal cord preparation and multiphoton microscopy in a dual-color system. Using this method, we are able to simultaneously monitor pre- and post-synaptic Ca^{2+} signaling from mice that express GCaMP3 in primary afferents and RGECO in dorsal horn neurons. We evaluated this signaling in a model of neuropathic pain, spared nerve injury (SNI), and sham controls, with pharmacological blockade of GABA and glutamate receptors to better clarify the roles of inhibition and excitation within primary afferent signaling. Our experiments demonstrate that the pre-stimulation of dorsal root A-fibers reduces the subsequent calcium elevation in electrically stimulated C-fibers and corresponding synaptic boutons in spinal dorsal horn laminae. Furthermore, the strength of C-fiber inhibition is directly proportional to the rate of electrically recruited Aβ-fibers. Additionally, as the electrical stimulation recruits low-threshold (LT) A-delta afferents, the strength of inhibition increases further. We also found that this presynaptic inhibition relies on both GABAergic and glutamatergic signaling. Overall, this study has contributed to our understanding of the first sensory synapse and its role in central sensitization. Crucially, we have demonstrated that both GABAergic and glutamatergic signaling regulate presynaptic Ca^{2}+ signaling.

Disclosures: A. Tokhtamysh: None. **Y. Andrianov:** None. **A. Keyes:** None. **P.V. Belan:** None. **N.V. Voitenko:** None. **Y.M. Usachev:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.25/AA7

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant

Title: Spinal Trpc4+ dorsal gray commissure interneurons gate bladder nociception and coordinate urethral sphincter control during micturition

Authors: *F. LIU[1], Y. ZHANG[1], M. KAWATANI[3], H. GREENHILL[2], L. YANG[4], M. HEITMEIER[1], V. K. SAMINENI[5];
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Abstract: Somatosensory signals from visceral end organs such as the urinary bladder are relayed to the spinal cord, yet the spinal mechanisms that process bladder sensation and coordinate voiding remain largely unclear. Here we identified a subpopulation of Trpc4-expressing interneurons in the lumbosacral dorsal gray commissure that are important for bladder sensation, pain, and micturition. Using a cell-type-specific genetic ablation approach, we found

that these neurons regulate both bladder pain and lower urinary tract function. Selective ablation of these neurons increased visceral hypersensitivity and altered voiding, producing more frequent, small-volume voids without affecting bowel output or somatic paw sensation, indicating a bladder-specific role. Simultaneous cystometry and external urethral sphincter electromyography in male mice showed that ablation disrupted the normal coordination of the sphincter during voiding: although the sphincter still engaged, the robustness of its bursting during micturition was degraded, consistent with impaired voiding. To define how these neurons are embedded in the micturition circuit, we used anterograde and monosynaptic retrograde viral tracing to map their inputs and outputs, revealing convergent input from supraspinal micturition centers including the ventromedial medulla and Barrington's nucleus. Together, these results establish this spinal Trpc4 population as an important node for encoding bladder pain and coordinating voiding, providing valuable insight into spinal processing of bladder sensory information and a potential target for visceral pain and voiding disorders.

Disclosures: F. Liu: A. Employment/Salary (full or part-time):; Washington University in Saint Louis. **Y. zhang:** None. **M. Kawatani:** None. **H. Greenhill:** None. **L. Yang:** None. **M. Heitmeier:** None. **V.K. Samineni:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.26/AA8

Topic: E.01. Somatosensation – Pain and Itch

Support: Hellman foundation

Title: Neuromodulatory effects of invasive and non-invasive stimulation on spinal cord hemodynamics in failed back surgery syndrome using functional ultrasound imaging

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Abstract: Chronic low back pain affects approximately 619 million people worldwide and is the leading cause of years lived with disability. A subset of spinal surgery patients develop failed back surgery syndrome (FBSS), persistent pain affecting up to 50%, frequently refractory to both pharmacological and surgical management, leaving spinal cord stimulation (eSCS) as a primary neuromodulatory option. Yet its efficacy remains inconsistent, primarily due to limited understanding of how stimulation modulates spinal neurodynamics. Its invasiveness further motivates the search for non-invasive alternatives such as peroneal nerve stimulation (PNS), whose effect on spinal cord hemodynamics remains unknown.We used functional ultrasound imaging (fUSI) to track spinal hemodynamics as an indirect readout of neural activity, acquiring

power Doppler (pD) recordings from FBSS patients (N=6) at T10 via laminectomy under general anesthesia. In each patient, eSCS and PNS were performed in one session with an identical imaging window. For eSCS, we delivered five 30s ON/OFF cycles (40 Hz, 250 μs) in bilateral and unilateral configurations. For PNS, we applied 3 cycles of 2-min ON/1-min OFF in left, right, and bilateral configurations. Responses were quantified with event-related averaging (ERA) and statistical parametric maps (SPMs).In a representative patient, eSCS evoked focal activation in the dorsal spinal cord across all laterality configurations, with spatially distinct increases and decreases in pD signal and clear biphasic ON/OFF dynamics. Laterality modulated response amplitude more than spatial distribution, with right unilateral stimulation evoking the largest response. PNS independently evoked measurable dorsal hemodynamic responses in the same patient, with laterality-dependent differences across left and right configurations. These findings demonstrate that both invasive eSCS and non-invasive PNS evoke detectable spinal cord hemodynamic responses, with laterality-dependent modulation, motivating further investigation of non-invasive spinal neuromodulation.

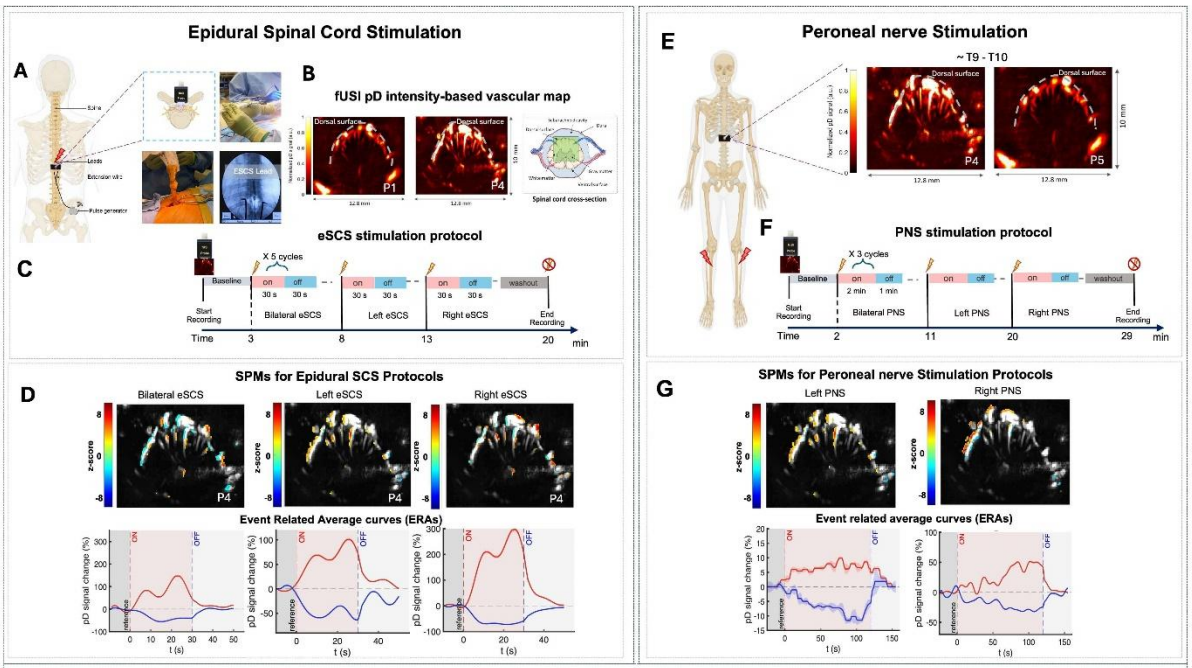


Figure 1. Functional ultrasound imaging of spinal cord hemodynamic responses to epidural spinal cord stimulation (eSCS) and peroneal nerve stimulation (PNS) in FBSS patients.
(A) Experimental setup for eSCS. Schematic of fUSI probe placement over the spinal cord at the laminectomy site, with intraoperative confirmation of epidural lead placement. **(B)** fUSI power Doppler (pD) intensity-based vascular maps of the spinal cord, showing the dorsal surface and surrounding vasculature (FOV 12.8 mm × 10 mm). A schematic spinal cord cross-section (right) for anatomical reference. **(C)** eSCS stimulation protocol. Following a 3-min baseline, stimulation was delivered in five 30-s ON/OFF cycles per configuration, applied sequentially in bilateral, left, and right configurations, followed by a washout period. **(D)** SPMs for eSCS protocols (top) showing pixel-resolved increases (warm) and decreases (cool) in pD signal relative to baseline across all configurations, overlaid on the grayscale vascular image. Corresponding ERA curves (bottom) show percent pD signal change during ON (red) and OFF periods, with positive (red) and negative (blue) responses. **(E)** Experimental setup for PNS. Non-invasive stimulation was applied unilaterally and bilaterally at the peroneal nerve below the knee, with fUSI recorded over the spinal cord at the same level as eSCS in the same patients (representative pD vascular maps shown). **(F)** PNS stimulation protocol. Following a baseline, stimulation was delivered in three 2-min ON/1-min OFF cycles per configuration, applied sequentially in bilateral, left, and right configurations, followed by a washout period (total recording ~29 min). **(G)** SPMs for PNS protocols (top) showing pD signal changes for left and right configurations, overlaid on the grayscale vascular image. Corresponding ERA curves (bottom) show percent pD signal change during ON and OFF periods.

Disclosures: H. Zareian: None. **K.A. Agyeman:** None. **D.J. Lee:** None. **C. Liu:** None. **V.N. Christopoulos:** None.

Poster

PSTR226: Pain: Spinal Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR226.27/AA9

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant P01AG066603
NIH Grant R01AG076783
NIH Grant R01AG068997

Title: Endplate osteoclast-derived netrin-1 drives a dorsal horn DCC amplification loop that generates nociplastic low back pain in male mice

Authors: *D. PAN[1], M. SHEN[2], J. ZHENG[2], J. ZHENG[2], Z. QIU[3], M. WAN[2], B. K. TAYLOR[4], X. CAO[2];
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Abstract: Chronic low back pain (LBP) is a leading cause of disability, yet most cases are "non-specific" with no identified pathoanatomical source, and disease-modifying therapies remain absent because the underlying circuit mechanisms are unknown. Using a lumbar spine instability (LSI) model and naturally aged male mice, we tested whether degeneration of vertebral endplates initiates and amplifies a pain circuit. We found that LSI and aging increased endplate porosity and the number of netrin-1$^+$/TRAP$^+$ osteoclasts, accompanied by CGRP$^+$ sensory innervation and elevated DCC expression in dorsal root ganglion (DRG) neurons; parallel increases in CGRP$^+$ fibers and DCC were observed in aged human endplates, where CGRP$^+$ fibers were ~3-fold more abundant than in young specimens. Conditional deletion of *Dcc* in Avil$^+$ sensory neurons, or of *netrin-1* in Trap$^+$ osteoclasts, reduced DRG hyperactivity (in vivo calcium imaging, cell-attached recording) and mechanical hypersensitivity. Mechanistically, netrin-1/DCC signaling drove Src phosphorylation and pSyt-1 binding, promoting SNARE complex assembly and presynaptic glutamate release from DRG terminals. This glutamate activated postsynaptic NMDA receptors in the dorsal horn (DH) and induced DH neurons to express both netrin-1 and DCC. DH-derived netrin-1, in turn, signaled back onto presynaptic DRG and postsynaptic DH neurons, establishing a self-reinforcing positive feedback loop that amplified spinal hypersensitivity; DH-specific netrin-1 knockout abolished LSI-induced behaviors and normalized DRG firing. Finally, fiber photometry revealed that netrin-1/DCC signaling and neuronal activity were further amplified in the parabrachial nucleus, and osteoclast-specific netrin-1 deletion attenuated this supraspinal activation along with pain behaviors. Together, these findings reveal a previously unrecognized endplate-to-brain signaling axis: osteoclast-derived netrin-1 initiates DCC-dependent sensory neuron sensitization that is amplified by a self-reinforcing dorsal horn circuit and relayed to the brain. This mechanism establishes non-specific LBP as a nociplastic disorder driven by central sensitization and nominates the netrin-1/DCC pathway as a therapeutic target for a disease that currently has none.

Disclosures: D. Pan: None. **M. Shen:** None. **J. Zheng:** None. **J. Zheng:** None. **Z. Qiu:** None. **M. Wan:** None. **B.K. Taylor:** None. **X. Cao:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.01/AA10

Topic: E.01. Somatosensation – Pain and Itch

Title: Effect of an immersive virtual reality and deep breathing intervention on pain and anxiety associated with peripheral venipuncture in adults. A randomized clinical trial

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Abstract: Background: Venipuncture is a common invasive clinical procedure that frequently causes discomfort due to acute pain and anticipatory anxiety. Cognitive and emotional components amplify this subjective discomfort, triggering sympathetic responses that lower the nociceptive threshold and pain tolerance. While local anesthetics exist, they often present adverse effects, and there is no clinical gold standard for the routine management of these symptoms, making non-pharmacological techniques highly relevant. Objective: To evaluate and compare the efficacy of virtual reality (VR) and deep breathing (DB) as non-pharmacological techniques for reducing pain and anxiety during venipuncture in adult participants. Design: A prospective, randomized, controlled clinical trial with three parallel groups and a blinded evaluator design. Methods: Conducted between February 2024 and March 2025 at a private healthcare institution in Mexico (Approval No. ICSa232/2024; Declaration of Helsinki). A total of 264 adults (18-65 years; mean age 35.3 +/- 11.8; 52.7% women) were randomly assigned to three groups: 1) VR group (n = 72) using immersive video virtual reality glasses; 2) deep diaphragmatic breathing group (n = 76) using synchronous diaphragmatic breathing; or 3) control group (CG, n = 116) receiving standard care (NOM-007-SSA3-2011). Pain (post-procedure VAS), anxiety (VAS; STAI-6 before and after), and blood pressure/heart rate (blood pressure monitor) were recorded. Data analysis included an ANCOVA adjusted for age as a covariate and Tukey's post hoc tests. Results: Baseline characteristics were homogeneous; 65.9% reported previous venipunctures. For the primary outcome (pain, VAS), the ANCOVA model revealed a significant main effect of the group factor. Tukey's analysis showed that the deep breathing (DB) group reported significantly lower pain scores compared to the control (CG) and virtual reality (VR) groups, with no difference between the latter two. Regarding anxiety, all three groups showed a significant within-group decrease (STAI-6), but final between-group comparisons showed no significant differences. Physiologically, VR reduced heart rate, while DB significantly decreased systolic and diastolic blood pressure. Overall satisfaction was high (61.4%), 42.4% preferred distraction, and only 16.6% of the VR group reported mild discomfort. Conclusion: Deep breathing stands out as a highly effective, safe, low-cost, and accessible non-pharmacological intervention for the management of acute pain during venipuncture, proving superior to immersive virtual reality and standard procedures in adults.

Disclosures: M. Ortiz Ramirez: None. **I. Ordoñez:** None. **L. Zamudio:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.02/AA11

Topic: E.01. Somatosensation – Pain and Itch

Title: Real-Time Modulation of Distributed Pain-Processing Networks with Breathing Controlled Electrical Stimulation (BreEStim)

Authors: *A. RAO[1,2], S. LI[1,2], H. MENG[1,2], M. HOUSTON[3,4], Y. ZHANG[3,4,5], S. LI[1,2]; [1]Dept. of Physical Med. and Rehabil., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [2]TIRR Mem. Hermann Hosp., Houston, TX; [3]Dept. of Biomed. Engin., Univ. of Miami, Coral Gables, FL; [4]Desai Sethi Urology Inst., [5]Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: Background: Breathing-controlled electrical stimulation (BreEStim™) synchronizes painful electrical stimulation with voluntary inspiration and has demonstrated analgesic effects; however, its neural mechanisms remain unclear. This study compared cortical responses during BreEStim and conventional electrical stimulation (EStim) using electroencephalography (EEG). Methods: Fourteen healthy adults (7 males, 7 females; age 31.8 ± 9.9 years) completed BreEStim and EStim sessions in a randomized crossover design. Repeated painful stimulation was delivered to the left median nerve at a perceived intensity of 6-7/10 for approximately 30 min. Event-related potentials (ERPs) and event-related spectral perturbations (ERSPs) were analyzed to characterize stimulus-locked and oscillatory cortical responses. Results: ERP analyses revealed significant intervention effects for the CP4 P1 ($p = 0.013$, $\eta p^2 = 0.414$), Cz P2 ($p = 0.047$, $\eta p^2 = 0.288$), and late positive potential (LPP; $p = 0.044$, $\eta p^2 = 0.295$). Compared with EStim, BreEStim produced smaller CP4 P1 and Cz P2 amplitudes but larger LPP amplitudes. ERSP analyses demonstrated reduced low-frequency activity during BreEStim, particularly in ACC delta and theta, S1 delta, and parietal delta bands (all pFDR = 0.007), alongside increased DLPFC gamma activity (pFDR = 0.029, $d = 0.797$). Conclusions: BreEStim alters cortical processing of painful stimuli despite equivalent pain perception. The findings suggest heightened cognitive-regulatory engagement and enhanced top-down modulation of distributed pain-processing networks.

Disclosures: A. Rao: None. **S. Li:** None. **H. Meng:** None. **M. Houston:** None. **Y. Zhang:** None. **S. Li:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.03/AA12

Topic: E.01. Somatosensation – Pain and Itch

Support: GRF Ref: 14119024
GRF Ref: 14119125
PHPRI grant Ref: 8423010
GRF Ref: 14117122

Title: Gut microbiota modulate descending sensorimotor cortex-spinal dorsal horn pathways to regulate pain hypersensitivity

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Abstract: Neuropathic pain is associated with maladaptive changes in descending pain modulation, but the cortical-spinal circuits that regulate spinal nociceptive processing remain incompletely understood. Here, we investigated whether peripheral nerve injury alters sensorimotor cortex-to-spinal dorsal horn communication and whether microbiota-based interventions can alleviate neuropathic pain hypersensitivity. Using retrograde viral tracing from the lumbar spinal cord dorsal horn, we identified multiple supraspinal inputs, including prominent projections from the hindlimb region of the primary somatosensory cortex, S1HL. Chemogenetic activation of the S1HL-to-spinal cord dorsal horn pathway in sham mice reduced mechanical withdrawal thresholds, increased pinprick responses, and shortened acetone-evoked withdrawal latency, indicating that this descending pathway facilitates behavioral responses to mechanical, noxious, and cold stimulation. In SNI mice, inhibition of the S1HL-to-spinal cord dorsal horn pathway increased mechanical withdrawal thresholds and reduced pinprick responses, suggesting that enhanced S1HL descending drive contributes to the maintenance of neuropathic pain hypersensitivity. Treatment with probiotics or fecal microbiota transplantation reduced mechanical and cold hypersensitivity in neuropathic pain mice. These behavioral improvements were accompanied by reduced overactivation of somatostatin-positive neurons in the spinal dorsal horn following noxious stimulation. Together, these findings suggest that neuropathic pain potentiates descending facilitation from S1HL to the spinal dorsal horn, thereby amplifying spinal nociceptive processing. Our study identifies the S1HL-spinal dorsal horn pathway as a cortical-spinal circuit mechanism contributing to neuropathic pain hypersensitivity and highlights microbiota-based interventions as a potential strategy for pain relief.

Disclosures: J. yanjun: None. **X. Liu:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.04/AA13

Topic: E.01. Somatosensation – Pain and Itch

Title: Δ9-Tetrahydrocannabiphorol and Δ9-Tetrahydrocannabinol differentially engage CB_1 receptor-dependent basal ganglia-brainstem control of nociception

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Abstract: Cannabinoid receptor type 1 (CB_1) is a key regulator of nociception within the central nervous system. However, its activation canonically results in the cannabinoid tetrad of effects, with catalepsy representing a limiting adverse effect of cannabinoid analgesics. Antinociception and catalepsy arise from distinct CB_1 receptor pools within the same striatonigral circuit: plasma membrane CB_1 receptors ($pmCB_1$) block nociception via substance P release suppression, whereas mitochondrial CB_1 receptors ($mtCB_1$) mediate catalepsy by inhibiting mitochondrial respiration. Analgesia-catalepsy coupling at overlapping doses is a hallmark of most synthetic cannabinoids and Δ9-tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa*. Δ9-Tetrahydrocannabiphorol (THCP) is a naturally occurring phytocannabinoid structurally related to THC, but distinguished by a heptyl side chain that confers a distinct receptor-binding profile. We therefore investigated whether these pharmacological differences translate into a distinct antinociceptive-cataleptic profile by comparing the effects of THCP and THC in WT, CB_1-*KO* and DN22-CB_1-*KI* mice lacking $mtCB_1$. THCP displayed dose-dependent cannabimimetic effects. While high doses produced the classical coupling of antinociceptive and cataleptic effects, low doses (<2.5 mg/kg, i.p.) strikingly dissociated them, revealing a therapeutic window not observed with THC. In isolated substantia nigra pars reticulata (SNr) mitochondria, low-dose THCP produced less inhibition of mitochondrial respiration than THC. THCP-induced antinociception was abolished in CB1-*KO* mice and preserved in DN22-CB_1-*KI* mice, consistent with a role for pmCB1-mediated signaling within the striatonigral pathway. To investigate the mechanism underlying the differential effects of THCP and THC, we explored the downstream circuits mediating cannabinoid-dependent analgesia, focusing on the periaqueductal grey-rostral ventromedial medulla (PAG-RVM) descending pain inhibitory pathway. Electrophysiological recordings revealed that low-dose THCP, but not THC, suppressed pronociceptive ON-cell activity in RVM. This effect was antagonized by pharmacological blockade of CB_1 receptors within either SNr or PAG. Notably, THCP retained efficacy across pain models, reducing nociceptive responses in the formalin test and producing antiallodynic effects in a model of central post-stroke pain. These findings identify THCP as the first Cannabis-derived CB_1 receptor agonist to dissociate antinociception from catalepsy in a dose-dependent manner, revealing a strategy for improved cannabinoid therapeutics.

Disclosures: R. Infantino: None. **M. Perrone:** None. **A. Pagano Zottola:** None. **R. Rodrigues:** None. **F. Ricciardi:** None. **C. Belardo:** None. **D.P. Finn:** None. **G. Cannazza:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Consiglio Nazionale delle Ricerche, Rome, Italy, Sapienza

University, Rome, Italy, University of Modena and Reggio Emilia, Italy. **S. Maione:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Consiglio Nazionale delle Ricerche, Rome, Italy, Sapienza University, Rome, Italy, University of Modena and Reggio Emilia, Italy. **G. Marsicano:** None. **L. Bellocchio:** None. **L. Luongo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Consiglio Nazionale delle Ricerche, Rome, Italy, Sapienza University, Rome, Italy, University of Modena and Reggio Emilia, Italy.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.05/AA14

Topic: E.01. Somatosensation – Pain and Itch

Title: Neuroinflammation along the SNpc-vlPAG-Spinal Cord circuit as a potential mechanism of neuropathic pain in hemiparkinsonism

Authors: *S. A. MEJIA AMADOR[1], F. J. PAZ[2], J. A. AVALOS, Jr.[3], J. RAYA TAFOYA[3], R. DELGADO-LEZAMA[3], G. B. FLORAN[4];
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Abstract: Neuropathic pain occurs in up to 85% of patients with Parkinson's disease; however, its mechanisms remain poorly understood. In models of neuropathic pain, spinal downregulation of the K^+-Cl^- cotransporter (KCC2) secondary to microglial hyperreactivity alters GABAergic activity in sensory neurons and interneurons of the dorsal horn, favoring nociception. Previously, our group demonstrated these alterations in a model of 6-hydroxydopamine (6-OHDA)- induced hemiparkinsonism; however, it is unknown how a basal ganglia (BG) injury generates the spinal changes observed. Since the ventrolateral region of the periaqueductal gray matter (vlPAG) is connected to the substantia nigra pars compacta (SNpc) and to the dorsal horn of the spinal cord (SCDH), and neuroinflammation in this region has been linked to pain generation, we propose that damage to the BG triggers a neuroinflammatory cascade in the SNpc-vlPAG-SCDH pathway, altering nociception in this model. In this study, male Wistar rats were injured in the right dorsolateral striatum with 6-OHDA, and the development of bilateral allodynia was corroborated with the Von Frey test. By immunofluorescence, in the SNpc, vlPAG and SCDH regions, the inflammatory cell markers Iba1+CD86/CD206, and GFAP were evaluated. Evaluations were performed at 7 and 15 days after injury, with day 7 being the onset of allodynia. In the SNpc of the injured hemisphere, progressive microglial activation was observed from day 7, with proinflammatory polarization and a significant anti-inflammatory reduction on

day 15, accompanied by astrocytic reactivity, as evidenced by increased cell number and morphological complexity, with no changes in the intact hemisphere. Continuing with vlPAG, generalized proinflammatory microglial activation was observed from 7 to 15 days. There was also an anti-inflammatory reduction and progressive astrocytic reactivity from 7 to 15 days. Finally, the same neuroinflammatory findings were observed in the SCDH, except that the reactivity was generalized, with no differences between the right and left horns or across time points. These results suggest that dopaminergic injury triggers a neuroinflammatory cascade along the SNpc-vlPAG-SCDH circuit, which could contribute to bilateral spinal GABAergic dysfunction and consequent bilateral neuropathic pain in the hemiparkinsonism model.

Disclosures: S.A. Mejia Amador: None. **F.J. Paz:** None. **J.A. Avalos:** None. **J. Raya tafoya:** None. **R. Delgado-Lezama:** None. **G.B. Floran:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.06/AA15

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5R01 NS133572 to DSM
NIH Grant 5T32 GM007281 to AA

Title: A Novel Pronociceptive Circuit Linking the Superior Colliculus to the Pedunculopontine Nucleus

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Abstract: Chronic pain remains a leading global health burden, as over 60 million Americans and 1.5 billion people worldwide are affected. Many patients are not adequately treated using current therapies, making chronic pain a primary driver of years lived with disability. In addition, the ongoing opioid crisis highlights the need to identify non-opioid treatments. Many current opioid and non-opioid analgesics relieve pain through modulation of the descending pain pathway, including the ventrolateral periaqueductal gray (vlPAG) and its projections to the rostral ventromedial medulla. Our recent findings indicate that cholinergic projections from the pedunculopontine nucleus (PPN) to the vlPAG bidirectionally modulate pain signaling. Acute and chronic pain conditions were found to suppress activity in PPN-vlPAG cholinergic projections, contributing to hyperalgesia. These observations highlight the need to understand the neural circuitry that ultimately controls these cholinergic projections. Previous studies indicate that the superior colliculus (SC) provides the densest afferent inputs to the PPN cholinergic neurons in rats. Using a pan-neuronal retrogradely-transported viral vector expressing the fluorophore GFP, we confirmed significant SC-PPN projections in mice (n=3). To assess the

functional role of SC-PPN projections, we employed a projection-specific chemogenetic strategy to activate SC-PPN neurons in mice, while monitoring nocifensive responses to noxious heat. Expression of excitatory G_q-coupled designer receptors exclusively activated by designer drugs (DREADDs) in the presynaptic inputs to PPN neurons was achieved by focal injections of a retrogradely-transported viral vector to express Cre recombinase in the PPN. A second viral vector carrying Cre-dependent G_q-DREADDs was then injected into the SC. Administration of the DREADD agonist, deschloroclozapine (DCZ, 0.1 mg/kg) 30 minutes prior to behavioral testing produced acute thermal hyperalgesia in a radiant heat source assay that resolved after 24 hours (n=4). Repeated once-daily DCZ-induced activation of these SC-PPN projections for 7 days induced thermal hypersensitivity that remained evident 24 hours after the final DCZ injection (n=3). These data suggest that activation of SC-PPN projections can enhance pain signaling, and that repeated activation of this pathway can promote persistent hyperalgesia. These findings identify SC-PPN projections as a novel pronociceptive circuit, and suggest that aberrant excitability in this pathway may contribute to chronic pain states. Better understanding of this pathway may help identify novel analgesic therapies.

Disclosures: A. Asadipooya: None. **Y. Yin:** None. **D.S. McGehee:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.07/AA16

Topic: E.01. Somatosensation – Pain and Itch

Support: No. R37 MH076136; Tor Wager

Title: Neural and Behavioral Evidence for Analgesic Effects of Motor Cortex tDCS

Authors: *A. DEHGHANI, D. GANTZ, M. KWON, T. D. WAGER;
Dartmouth Col., Hanover, NH

Abstract: Title: Neural and Behavioral Evidence for Analgesic Effects of Motor Cortex tDCS**Authors:** Amin Dehghani [1], David M. Gantz [1], MijinKwon[1], Tor D. Wager [1]
[1]Department of Psychological and BrainSciences, Dartmouth College, Hanover, NH, USATranscranial direct current stimulation (tDCS) of the primary motor cortex (M1) has shown promise for pain modulation, but the neural mechanisms underlying its analgesic effects remain incompletely understood. We investigated the behavioral and neural effects of anodal, cathodal, and sham M1-tDCS in a double-blind, randomized, within-subject crossover study. Twenty-seven healthy participants completed three experimental sessions following individualized thermal pain calibration. Dynamic thermal pain stimuli were delivered before and after 20minof M1-tDCS (2mA; C3-FP2montage). Functional MRI data were acquired following stimulation and analyzed using fMRIPrep, tedana, and CANlab tools. Pain-related neural responses were quantified using the Neurologic Pain Signature (NPS) and Stimulus Intensity Independent Pain

Signature (SIIPS). Mixed-effects analyses revealed a significant reduction in post-stimulation pain ratings following anodal stimulation relative to cathodal and sham conditions ($F(1, 22)= 47$, $p< 0.001$), whereas cathodal and sham stimulation did not differ. Consistent with these behavioral effects, anodal stimulation significantly reduced NPS expression relative to cathodal stimulation ($t(26)= -2.9$, $p< 0.01$) and reduced SIIPS expression relative to sham stimulation($t(26)= -3.6$, $p< 0.01$). Analyses restricted to high-intensity thermal stimuli demonstrated significant reductions in both NPS and SIIPS responses following anodal stimulation compared with cathodal and sham conditions. No significant differences were observed between cathodal and sham stimulation. These findings indicate that anodal M1-tDCS modulates both nociceptive and higher-order pain-related neural representations while simultaneously reducing subjective pain experience. The results provide converging behavioral and neuroimaging evidence that motor cortex stimulation influences multiple dimensions of pain processing and support the use of pain-related brain signatures as mechanistic biomarkers of neuromodulation-induced analgesia.

Disclosures: A. Dehghani: None. **D. Gantz:** None. **M. Kwon:** None. **T.D. Wager:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.08/AA17

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Neurological Surgery University of Virginia School of Medicine

Title: Disentangling descending inhibition from habituation in conditioned pain modulation

Authors: A. JACOBSON[1], P. REALYVASQUEZ[1], D. WANG[1], S. RAVIKANTI[1], ***C.-C. LIU**[2];
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Abstract: Conditioned pain modulation (CPM) is commonly interpreted as a behavioral index of endogenous descending inhibition, in which pain evoked by a noxious test stimulus is attenuated during a spatially remote noxious conditioning stimulus. However, most CPM protocols use a fixed baseline-to-conditioning sequence, so reduced pain during the conditioning block may reflect descending inhibition, habituation to repeated test stimulation, or both. This distinction is important because a larger CPM effect in the standard order could be misinterpreted as stronger inhibition when it partly reflects adaptation to repeated test stimulation. We developed a laser-based CPM paradigm with standard, reversed, and no-conditioning control orders to examine how block order and repetition-related habituation contribute to CPM-related pain reduction. Thirty healthy adults completed three conditions. Test stimuli were brief Nd:YAP infrared laser pulses, 1.34 μm, 4 ms, which preferentially activate cutaneous Aδ nociceptive afferents and

provide temporally discrete noxious input. Pain intensity was rated on a 0-100 visual analog scale. The conditioning stimulus was right-hand immersion in circulating 0°C ice water. In Standard, a baseline laser block was followed by a CPM block in which laser stimuli were delivered during ice-water immersion. In Reversed, the CPM block preceded baseline. In Control, participants completed two baseline laser blocks without conditioning. This design allowed CPM effects to be tested in both temporal directions while estimating habituation using the same laser test stimulus in the absence of conditioning. Laser pain ratings were reduced during CPM relative to baseline in both Standard, $p<0.001$, and Reversed, $p=0.007$, indicating that CPM-related pain reduction was preserved when the conditioning block occurred first. CPM magnitude differed by order, $p=0.018$, with a larger apparent effect in Standard. In Control, pain ratings also decreased across repeated baseline blocks, $p=0.015$, demonstrating habituation in the absence of conditioning. The present results indicate that CPM-related pain reduction is not solely explained by repeated testing, but that standard baseline-to-CPM sequencing can amplify apparent CPM magnitude through habituation. Brief laser test stimulation, combined with reversed-order and no-conditioning control conditions, provides a useful approach for separating descending inhibitory modulation from habituation-related decreases in pain.

Disclosures: A. Jacobson: None. **P. Realyvasquez:** None. **D. Wang:** None. **S. Ravikanti:** None. **C. Liu:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.09/AA18

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R03-DA058194

Title: Characterizing Enkephalinergic Circuits and Opioid Peptide Expression During Pain

Authors: *G. R. DURRANT[1], C. PORTER[2], E. N. BOBECK[2];
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Abstract: Characterizing Enkephalinergic Circuits and Opioid Peptide Expression During Pain
Greydon R. Durrant, Callie M. Newson, Oakley M. Statham, Lucy N. Scribner, MaKenzie Long, Erin N. Bobeck
The endogenous opioid system plays an important role in modulating pain through the descending pain pathway. While opioid receptors and pharmaceuticals have been widely studied, less is known about how endogenous opioid peptides and their associated circuits contribute to processing pain. Additionally, it remains unclear how opioid peptide and receptor expression changes across different pain states and between sexes. To begin addressing these questions, we used retrograde tracing in PENK-IRES2-Cre mice to identify sources of enkephalinergic input to the ventrolateral periaqueductal gray (vlPAG), a critical hub for descending pain modulation. We

found that the PFC, ACC, AMG, VTA, and RVM all send enkephalinergic projections to the vlPAG. We selected these regions to investigate due to their previously documented roles in pain processing. To investigate the functional role of this circuit, excitatory DREADDs were used to selectively activate vlPAG-projecting enkephalinergic neurons. Chemogenetic activation significantly increased antinociception in both male and female mice during plantar and formalin pain assays (all $p < 0.05$), with comparable effects observed across sexes, showing this circuit plays a role in modulating acute pain. Opioid peptide signaling across pain-related brain regions was further characterized using quantitative PCR to measure proenkephalin gene (PENK) expression. We found PENK expression was significantly higher in the NAc compared to the PAG in both males ($p = 0.0098$) and females ($p < 0.0001$). Females also showed significantly greater PENK expression in the AMG compared to males ($p = 0.03$), suggesting both region- and sex-dependent differences in enkephalin signaling. Since these findings reveal baseline differences in opioid peptide expression, we wanted to understand how chronic pain might alter this pattern. We are now investigating how CFA-induced chronic inflammatory pain affects expression of opioid peptide genes (PENK, PDYN, POMC) and opioid receptor genes (OPRM1, OPRD1, OPRK1) across pain-related brain regions in both male and female mice. Together, these findings improve our understanding of how enkephalinergic circuits and opioid peptide expression contribute to pain modulation. Studying expression of endogenous opioid peptides and receptors allows us to better understand the brain's response to pain. This information lays critical groundwork for the potential creation of future targeted pain therapies.

Disclosures: G.R. Durrant: None. **C. Porter:** None. **E.N. Bobeck:** None.

Poster

PSTR227: Descending Pain Modulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR227.10/AA19

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant ZIACL090033
NIH Grant ZIACL090034
NIH Grant ZIACL090035

Title: Thalamic Spatial Transcriptomics Reveals Mu and Kappa Opioid Receptor Circuits Involved in Pain and Addiction

Authors: *O. BLIVIS[1,3], M. R. SAPIO[4], M. L. WEISS[6], S. SHAH[5], D. MARIC[7], A. J. MANNES[2], M. J. IADAROLA[4];
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Abstract: Chronic pain is an enduring, aversive state that imposes significant negative emotional and behavioral consequences. This state is the result of integrating diverse nociceptive signals into a unified experience of pain involving multiple cortical regions in addition to the sensory discriminative elements processed in primary somatosensory cortex (S1). The endogenous opioid system modulates pain inputs and reward circuits, however, its relationship to cognitive processes of pain is not clearly defined. Here we focus on the mediodorsal (MD) nucleus, a thalamic hub which is known to have dense reciprocal connections with anterior cingulate (ACC) and prefrontal (PFC) cortices. These networks assign salience, regulate affect, and guide decision-making, and through further connections to hippocampus and amygdala, memory and emotional aspects of pain. Using spatial transcriptomics, we identify a large population of MD excitatory neurons that express the μ- and κ- opioid receptors and the neuropeptides CART (cocaine- and amphetamine-regulated transcript) and neurotensin. The glutamatergic CARTPT-expressing neurons are transcriptionally distinct from MD GABAergic neurons. We hypothesize that glutamate-CART peptide signaling from MD neurons drives cortical computations underlying valuation, avoidance, cognitive control and cue selection/reinforcement. These behavioral domains have a strong relationship to substance use disorders and addiction in addition to pain, and may form a node of convergence between the two neurobiological constructs. The results provide the first spatially resolved molecular map of an opioid receptor-modulated MD circuit, revealing previously unrecognized peptide-defined excitatory subnetworks with potential roles in affective and motivational dimensions of pain.

Disclosures: O. Blivis: None. **M.R. Sapio:** None. **M.L. Weiss:** None. **S. Shah:** None. **D. Maric:** None. **A.J. Mannes:** None. **M.J. Iadarola:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.01/AA20

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 DC021542

Title: Refractive index matching improves image resolution in the mouse cochlear whole mount fluorescent microscopy

Authors: N. AOKI, *T. MAKISHIMA;
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Abstract: Cochlear whole-mount preparations preserve tonotopic information and enable region-specific assessment of the organ of Corti. However, tissue thickness and light scattering can limit cell-type specific visualization in fluorescent microscopy, often requiring confocal or lightsheet imaging. We tested whether an immunohistochemistry combined with tissue clearing workflow improves visualization of neurofilament, a major component of afferent projections

from sensory hair cells, in the mouse cochlear whole-mount specimen.Cochleae were dissected from adult C57BL6 mice and processed using three workflows: conventional immunohistochemistry (Conv-IHC), Conv-IHC followed by ScaleS4-based refractive index matching (IHC+S4), and a Scale-compatible IHC workflow (Scale-IHC). For Conv-IHC, samples were labeled with anti-Neurofilament H antibody, Phalloidin (F-actin) and DAPI (nuclei), and mounted in an aqueous mounting medium. IHC+S4 samples underwent same IHC protocol, equilibrated, and mounted in modified ScaleS4 medium. Scale-IHC samples underwent Scale-compatible aqueous tissue-clearing workflow (Hama et al., Nat Neurosci. 18(10):1518-29. 2015). Samples were imaged with a fluorescent microscope under the same acquisition settings. Neurofilament visualization was quantified using the signal-to-background ratio (SBR) and contrast-to-noise ratio (CNR). SBR was calculated as the mean neurofilament-positive signal divided by the mean local background, and CNR as the signal-background difference divided by the standard deviation of the local background. SBR did not consistently increase after IHC+S4 or Scale-IHC. In contrast, CNR showed region-dependent changes. In the outer hair cell (OHC) region, IHC+S4 improved CNR compared with Conv-IHC. In the inner spiral bundle (ISB) region, improved CNR was observed in both IHC+S4 and Scale-IHC samples. In the osseous spiral lamina (OSL) region, F-actin staining revealed vascular-like structures more clearly in Scale-IHC samples. These findings suggest that IHC+S4 and Scale-IHC improve neurofilament fiber visibility mainly by enhancing local contrast and reducing background noise, rather than by increasing absolute fluorescence intensity. Improved CNR in the ISB region and clearer F-actin-positive structures in the OSL suggest that the combined approach was more effective in thicker and optically complex cochlear regions. We conclude that Scale-compatible refractive index matching improves cochlear whole-mount imaging in conventional fluorescence microscopy.

Disclosures: N. Aoki: None. **T. Makishima:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.02/AA21

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC013181
American Hearing Research Foundation

Title: Further characterization (morphological, quantitative and proteomic) of inner ear mitochondria

Authors: *A. LYSAKOWSKI[1], F. IMRAN[1], M. HAMEED[1], J. ORUGANTI[1], Z. BAIG[1], M. AZIZ[1], S. SAVYA[2], E. SANCHEZ[1];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Illinois Math and Sci. Acad., Aurora, IL

Abstract: Background: In this study, we quantified multiple aspects of mitochondrial structure in the inner ear. Our main hypothesis in this research is that inner ear mitochondria are structurally heterogeneous, depending on which hair cell (HC) type is under consideration and the specific locations of mitochondria in relation to other organelles. One such structural relationship is the polarization of mitochondrial crista junctions (CJs), openings of the internal mitochondrial membrane into the intermembrane space that are likely responsible for transport of molecules from the mitochondrial matrix out to the cytoplasm. Proteomic analyses aim to discover whether the different types of mitochondria have different sets of proteins. **Methods:** Inner ear vestibular tissue obtained from Long-Evans rats under an approved UIC IACUC procedure was used for electron microscope tomography. Data were processed with IMOD (v.3.13.6) software (Kremer et al., 1996) and serial tomograms were joined using the etomo subroutine (IMOD). Manual segmentation was done with the 3dmod subroutine (IMOD) to obtain final models. Reconstructions were visualized using 3dmod to track relevant features in 3 dimensions. Several IMOD drawing tools (Sculpt, Join, Warp, Interpolator) and a proximity analysis tool (MTK) with a randomization feature, were also used. Proteomic analyses have also been performed on the 3 different size classes. **Results:** Quantitative analyses were performed, including total mitochondrial counts in both vestibular HC types (compared to cochlear HCs), efferent boutons, and afferent calyces, counts of CJs on either side of a mitochondrion relative to other organelles, analyzing polarization ratios vs distances, bioenergetic calculations of ATP production, and an MTK test using CJ randomization as a control. Results support our hypothesis of structural heterogeneity of mitochondria, as CJs are polarized toward specific cellular organelles and appear to be non-randomly distributed. Finally, vestibular HCs have less than half the number of mitochondria in cochlear HCs, although some are larger than cochlear mitochondria. **Conclusions:** The structural differences have functional implications. CJ polarization toward organelles that use energy can transport ATP more efficiently, e.g., the cuticular plate is an organelle that functions to return stereocilia back to their original position. Our results show a non-random orientation of mitochondrial CJs toward the cuticular plate. These structural differences may provide key information to better understand their function and to address mitochondrial deafness and dizziness disorders.

Disclosures: A. Lysakowski: None. **F. Imran:** None. **M. Hameed:** None. **J. Oruganti:** None. **Z. Baig:** None. **M. Aziz:** None. **S. Savya:** None. **E. Sanchez:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.03/AA22

Topic: E.05. Auditory and Vestibular Systems

Support: Utica University Student Grant 1101-311002-771803-13

Title: The Effects of Caffeine and Melatonin on the Vessels of Mouse Stria Vascularis

Authors: *E. VARGAS, T. PROVOST, A. K. PACK;
Biol., Utica Univ., Utica, NY

Abstract: The stria vascularis (SV) supports the establishment of the endocochlear potential, which is vital for normal cochlear function; it is located on the lateral wall of the cochlea. The SV is composed of three cell layers, and capillaries can be found sandwiched between the first two. The purpose of this study was to investigate the effects of caffeine or melatonin on the vasodilation and vasoconstriction of these vessels. We treated three groups of Swiss Webster mice (n = 4/group) with water containing either 10mg/L melatonin, 0.5g/L caffeine, or nothing (control) for a period of 4 weeks. Cochleae were harvested and preserved with 3% paraformaldehyde and 0.1% glutaraldehyde, and embedded in Araldite (Durcupan). The tissue was then sectioned and stained with methylene blue. Images of midmodiolar sections were recorded for offline measurement and analysis with ImageJ. No significant effect of either treatment was demonstrated for cross-sectional vessel area between any groups (Kruskal-Wallis test, P = 0.212).

Disclosures: E. Vargas: None. **T. Provost:** None. **A.K. Pack:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.04/AA23

Topic: E.05. Auditory and Vestibular Systems

Support: NIH-NIDCD R21 DC022412
NIH-NIDCD R01 DC012347

Title: Local Coupling in Vestibular Epithelia Synchronizes Afferent Signals

Authors: *A. GOVINDARAJU, R. RAPHAEL;
Rice Univ., Houston, TX

Abstract: Type I hair cells within vestibular sensory neuroepithelia rapidly transduce head motion into electrical signals that inform gaze, orientation, and balance. Type I cells can transmit, without vesicle release, to cup-like afferent neuron terminals by directly altering synaptic cleft potassium ion concentration and electrical potential to modulate postsynaptic currents (Govindaraju et al., 2023, PNAS). Here, we present investigations performed using a computational model that considers multiple type I hair-cell-afferent complexes within tightly packed epithelium and evaluates the impact of local electrical coupling on AP synchrony in the outgoing neuronal processes. To simulate hair-cell-afferent transmission and electrical coupling within the epithelium, our model uses Hodgkin-Huxley-style ion currents and continuity equations to describe changes in electric potential within hair cells, afferent fibers, and intercellular spaces. Electro-diffusion equations are used to model [K+] and [Na+] in synaptic clefts and other intercellular spaces. Hair-bundle deflection or voltage-step protocols are used as

inputs. Simulations were performed in COMSOL 6.4 software using physiologically representative finite-element geometries that included multiple cells within an epithelium and multiple parallel edges representing outgoing neuronal processes. Compound action potentials were calculated as a function of currents entering and dispersing into a uniform medium surrounding the multiple neuronal processes during the propagation of APs generated by the epithelial model. Cell conductance and neuronal process geometry parameters were varied using normal distributions to test the effects of cell-to-cell variability on the timing of the vestibular compound action potential with and without local electrical coupling within the epithelium. We find that collective stimulation of adjacent hair cells (as occurs in vivo) reduces AP latency. Our results also show that the proximity and electrophysiology of cells in the vestibular epithelium permit coupling through changes in intercellular electrical potentials and thereby facilitate fast, synchronous spiking in adjacent neuronal processes projecting to the central nervous system. Our models predict that such coupling is an underlying factor in the low temporal spread of the vestibular compound action potential. Further development of both models will permit intraoperative assessment of epithelial function and evaluation of vestibular implant stimulation paradigms. Supported by NIH-NIDCD (R21 DC022412 to A.C.G. and R01 DC012347 to R.M.R.)

Disclosures: A. Govindaraju: None. **R. Raphael:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.05/AA24

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC018304
R01DC012347
F31DC021883
CBC-AG-002
1R90DA060338
R01DC023609

Title: The coherence of vestibular hair cell population responses depends on stimulus frequency, epithelial location, and hair cell type

Authors: *C. K. LUONG[1], M. KABIROVA[2], O. LUTZ[1], K. ZHANG[1], J. B. GIDEONS[1], D. SILVIAN[1], R. EATOCK[3];
[2]Mol. Biol., [3]Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: The mammalian utricle detects head tilt and linear acceleration through populations of hair cells in the sensory epithelium, but how linear head motions are represented in time and space across the epithelium has not been visualized. To address this question, we measured

calcium activity in mouse utricular hair-cell populations driven simultaneously by a fluid jet delivering sine bursts from 0.1-20 Hz. Hair-cell responses were mapped onto reconstructed utricles, allowing comparisons among striolar (S), lateral extrastriolar (LES), and medial extrastriolar (MES) epithelial zones as well as between type I and type II hair cells. Unit recordings from hair cells and afferents have shown physiological differences between zones and hair-cell types. Here we examine the coherence of hair-cell activity to better understand vestibular afferent input during head motions. Results are from animals aged P8-P21. Stimulus-response (SR) coherence quantified the fidelity with which hair-cell populations encoded the applied fluid-jet stimulus, while response-response (RR) coherence measured temporal coordination among hair cells within defined populations. Both SR and RR coherence declined above approximately 5 Hz, likely reflecting biological temporal filtering and the kinetics of calcium signaling and the GCaMP8m indicator. However, coherent spatial organization remained evident through 10 Hz. At 1-2 Hz, striolar (S) populations exhibited modestly greater SR and RR coherence than extrastriolar populations, whereas lateral (LES) and medial (MES) extrastriolar regions were largely similar. At 5 and 10 Hz, zonal differences became more pronounced, with S populations exhibiting the highest coherence, LES populations intermediate coherence, and MES populations the lowest coherence in both SR and RR analyses. Coherence was also sensitive to cell type: for example, S type I cells had higher SR and RR coherence than ES type I cells.
These findings demonstrate that mechanically evoked calcium signals are organized into frequency-dependent spatial and cell type ensembles across the utricular sensory epithelium. Population calcium imaging provides a framework for understanding how epithelial zones and hair-cell specialization shape the collective encoding of head motion prior to transmission to vestibular afferents.

Disclosures: C.K. Luong: None. **M. Kabirova:** None. **O. Lutz:** None. **K. Zhang:** None. **J.B. Gideons:** None. **D. Silvian:** None. **R. Eatock:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.06/AA25

Topic: E.05. Auditory and Vestibular Systems

Support: 1F31DC022140-01A1

Title: Regulation of hearing by differential localization of P4-ATPases in the developing mouse cochlea

Authors: *K. NIMCHUK, A. HASAN, H. DE HOYOS, J.-B. SHIN;
Univ. of Virginia, Charlottesville, VA

Abstract: Hearing is a fundamental sensory process that depends on sensory hair cells (HCs) conveying sound information to the brain via the afferent spiral ganglion neurons (SGNs). Synaptic connections between HCs and SGNs are therefore essential to hearing. HC-SGN synapses may be regulated by plasma membrane composition, and the externalization of specialized phospholipids, like phosphatidylserine (PS) on the outer leaflet of the membrane can mark these connections for removal via phagocytosis. Regulation of PS to the inner leaflet of the cell membrane is driven by a class of proteins called flippases, which "flip" phospholipids from the extracellular to the cytosolic leaflet. Flippases are therefore necessary for the long-term survival of HCs and SGNs. In early postnatal development, SGNs form excessive synapses with HCs which must then be pruned. We hypothesized that this pruning could be due to phagocytosis of the excess synapses and thus may be regulated by flippases. Consequently, we screened the localization of flippases known to be expressed in the cochlea and found one, ATP8A2, that undergoes a substantial change in localization during the pruning period. We hypothesized that the change in localization of ATP8A2 is due to the mechanotransduction (MET) activity of HCs, which is also maturing during this developmental time. To test this, we knocked out (KO) Cib2, an essential component of the MET complex, and found that both ATP8A2 localization and the number of HC-SGN synapses is significantly disrupted. To determine whether ATP8A2 itself is necessary for proper synapse pruning, we counted HC-SGN synapses in both a hypomorphic mouse model and in a full KO mouse model of ATP8A2. Though both mice had hearing loss by one month old, neither genotype impacted synapse count or SGN density at the conclusion of pruning. We suspected that ATP8A1, another flippase with similar localization to ATP8A2 could have a redundant role in cochlear development, but double KO of *Atp8a1* and *Atp8a2* is embryonic lethal. We instead crossed our hypomorphic ATP8A2 mouse to the ATP8A1 KO. While we expect that this mouse line will be useful to other researchers interested in the role of ATP8A1 and ATP8A2 in other systems, we found that there was not a difference in the number of synapses in the double mutant mice compared to controls. Nevertheless, our data provide an overview of the localization of cochlear flippases and offer further evidence that MET is essential for the proper development of HC synapses. We thus provide mechanistic insight into early postnatal development and synaptic pruning of the cochlea.

Disclosures: K. Nimchuk: None. **A. Hasan:** None. **H. De Hoyos:** None. **J. Shin:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.07/AA26

Topic: E.05. Auditory and Vestibular Systems

Support: NIDCD R01 DC019359
NIDCD F31 DC020882
David M. Rubenstein Hearing Research Fund

Title: Loss of Zbtb20 Disrupts Cochlear Sensory Epithelium Patterning and Maturation and Extends the Postnatal Hair Cell Regenerative Window in Mice

Authors: *C. MORGAN, A. DOETZLHOFER;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The transcription factor *Zbtb20* is mutated in Primrose syndrome, a rare developmental disorder that can cause progressive hearing loss. A recent study (Xie et al. 2023 *PNAS*) using a conditional knockout (cKO) mouse model of *Zbtb20* reported profound hearing loss and atypical maturation of the nonsensory lateral cochlear epithelium. Here, we report a similar hearing phenotype using two novel *cre*-mediated cKO strategies. This hearing phenotype was observed in both the $Emx2^{cre}$ mouse model, which induces *Zbtb20* KO in the entire cochlear duct, and the $Tecta^{cre}$ mouse model, which restricts the cKO domain to the sensory epithelium and Greater Epithelial Ridge (GER), implicating not only the lateral nonsensory region but also the sensory epithelium in the mechanism of observed hearing loss. Using the cochlear-duct specific $Emx2^{cre}$model, we also show delayed differentiation and maturation within the sensory epithelium and subsequent defects in Hair Cell (HC) and Supporting Cell (SC) numbers and patterning. $Emx2^{cre}$*;Zbtb20* cKO mice exhibited patterning defects in the cochlear sensory epithelium, specifically an increase in outer HCs (OHCs) and Deiter's Cells. Notably, the apical tip showed no tapering of OHC rows, instead producing a blunt end with 4 rows of OHCs. $Emx2^{cre}$*;Zbtb20* cKO sensory epithelia also showed a mild delay in neuronal innervation at postnatal day 0 (P0), and RNAseq and immunolabeling at P5 showed downregulation of key SC subtype-specific genes, such as *Fabp7* in Hensen's Cells, and an upregulation of the stemness-related genes *Hmga2* and *Sox11*. Finally, we evaluate the HC regeneration capacity of cochlear SCs *in vitro*, revealing an increased regenerative capacity of the developmentally immature $Emx2^{cre}$;*Zbtb20* cKO sensory epithelium. Profiling of the $Emx2^{cre}$*;Zbtb20* cKO SCs using a P5 organoid culture model showed increased organoid size and formation efficiency, increased proliferation, and increased HC regeneration. HC regeneration via SC transdifferentiation was also observed in organotypic P5 $Emx2^{cre}$*;Zbtb20* cKO cochlear explants in both the presence and absence of Diphtheria Toxin-mediated HC damage. Altogether, this study reveals *Zbtb20* as a master regulator of cochlear development and maturation in both the sensory and non-sensory epithelium. Loss of *Zbtb20* leads to profound hearing loss, SC and HC patterning defects, and a delay in SC maturation, and the developmentally immature state of SCs increased organoid formation and HC regeneration *in vitro*. Further study is needed to localize the cellular mechanism of the observed hearing phenotype originating from the sensory epithelium.

Disclosures: C. Morgan: None. **A. Doetzlhofer:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.08/AA27

Topic: E.05. Auditory and Vestibular Systems

Support: Chicago Biomedical Consortium (MK)
American Otological Society Research Training Fellowship (MK)
R01DC023609 (all)
R01DC012347 (all)
R01DC018304 (CKL, MK, RAE)
TPCN 1R90DA060338 (KZ)

Title: Age-related vestibular hair cell changes and balance decline in mice

Authors: *M. KABIROVA[1], J. B. GIDEONS[1], K. ZHANG[1], C. K. LUONG[2], R. EATOCK[2]; [2]Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: Aging is associated with a decline in vestibular function, leading to balance issues and an increased risk of falls in older individuals. While there has been an emphasis on the role of the central nervous system (CNS) in loss of stability with age, the integrity of the vestibular inner ear is vital for providing accurate head-motion signals to the CNS. Histological studies on human tissues report age-related reduction in hair cell density in all vestibular organs (Richter, 1980; Merchant et al., 2000). Recent work shows that impaired vestibular function in a mouse model of ototoxicity correlates with vestibular hair cell (VHC) loss: impairment begins to show at 20% HC death and is complete by 50% (Schenberg et al., 2025). We are interested in whether aging VHCs show dysfunction before cell death and whether therapeutic intervention could rescue them.To address these questions, we are using a Vglut3-GCaMP8m mouse line in which every VHC constitutively expresses a calcium indicator. This enables population-level calcium imaging during mechanostimulation to capture functional changes in the vestibular periphery. Building on our finding that response-response coherence differs between zones (striola vs. extrastriola; Luong et al., this meeting), we are investigating how aging shapes evoked activity across the utricular epithelium. From baseline GCaMP8m fluorescence we can image all hair cells in the intact sensory epithelium allowing us to count hair cells by type and epithelial location without immunolabeling. We developed a two-photon imaging pipeline with automated segmentation and registration to a canonical utricular map for this purpose. To evaluate the functional impact of vestibular changes at the behavioral level, we are testing young adult (4-6 months) and aged (14-16 months) mice for narrow-beam crossing, swimming, and open-field exploration. Aged mice required significantly more time to traverse a narrow beam and frequently slipped and showed other forms of imbalance. These are likely to be vestibular-specific deficits rather than motor deficits, given that open-field activity did not show a difference between groups. With this program, our goal is to trace age-related vestibular dysfunction from hair cell physiology to animal behavior.

Disclosures: M. Kabirova: None. **K. Zhang:** None. **C.K. Luong:** None. **R. Eatock:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.09/AA28

Topic: A.07. Development of Neural Systems

Support: NIDCD R01DC011571
NIDCD R01DC019359
Action on Hearing Loss Discovery Grant G99
David M. Rubenstein Fund for Hearing Research
Center for Hearing and Balance T32 Training Grant

Title: Characterizing the Role of NFI Transcription Factors in Hair Cell Differentiation and Type II Subtype Specification in the Murine Utricle

Authors: *E. VENHAUS, A. DOETZLHOFER;
Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: The utricle contains two subtypes of mechanosensory hair cells, type I and type II, whose proper specification is essential for vestibular function. Here, we investigate the role of Nuclear Factor I (NFI) transcription factors in utricle development. We show that NFIB is broadly expressed in supporting cells and progenitors, while NFIA and NFIX become progressively restricted to type II hair cells during postnatal maturation, suggesting subtype-specific transcriptional programs emerge postnatally. To interrogate NFI function, we generated embryonic conditional knockouts of NFIA, NFIB, and NFIX using the Tecta-Cre line. Loss of these factors at E14.5 results in delayed stereocilia formation at E18.5/P0, and supporting cells show delayed cell cycle exit, implicating NFIs in the timely differentiation of hair cells. Hair cell numbers and phalloidin-labeled bundles appear grossly normal by P15, indicating that NFIs are not required for hair cell survival but rather for the early progression of hair cell differentiation. Additionally, we find that embryonic deletion of NFIA/B/X reduces SOX2 expression in hair cells, which has independently been shown to drive loss of type II character. Consistent with a shift toward type I fate, the density of Tuj1+ calyces is increased by P5 in knockout mice. Finally, postnatal deletion of NFIA/B/X in type II hair cells using a Sox2-Cre driver also leads to SOX2 downregulation without hair cell loss, demonstrating that continued NFI expression is necessary to sustain type II identity after specification is complete. Overall, these findings establish NFI transcription factors as regulators of both the early differentiation of hair cells and the specification and maintenance of type II subtype identity in the utricle.

Disclosures: E. Venhaus: None. **A. Doetzlhofer:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.10/AA29

Topic: A.07. Development of Neural Systems

Title: The role of Notch ligand Jagged1 in prosensory specification

Authors: *R. HUANG, A. DOETZLHOFER;
Johns Hopkins Univ., Baltimore, MD

Abstract: Abstract: Objective Mechano-sensory hair cells within the inner ear cochlea are essential for sound detection. The Notch ligand Jagged1 (Jag1) is critical for the specification and maintenance of the cochlear prosensory domain, from which both hair cells and supporting cells derive. Mutations in the JAG1 gene cause hearing loss in both humans and mice, underscoring the need to clarify JAG1's role in cochlear development. However, the molecular mechanisms by which JAG1 regulates prosensory domain specification and maintenance remain largely undefined. Additionally, the specific Notch receptors that mediate JAG1's function in the developing cochlea remain unknown.**Methods** The role of JAG1 in mouse cochlear prosensory specification was investigated using a conditional knockout approach to disrupt JAG1 function during embryogenesis. To evaluate the function of candidate JAG1 receptors, supporting cell-specific Notch1/Notch2 double conditional knockout mice were generated. Phenotypic analyses included immunofluorescence and transcriptomic profiling.**Results** (1) Characterization of JAG1-regulated transcriptome in pro-sensory cells, which included known regulators of pro-sensory specification. (2) Identification of Cdkn1b (p27/Kip1), which is essential for the pro-sensory cell cycle, as a key target of JAG1-mediated regulation. (3) Conditional deletion of Jag1 in prosensory cells disrupted their apical-to-basal gradient of cell cycle exit. (4) Identification of Notch1 and Notch2 as the Notch receptors that mediate JAG1’s function in prosensory cell specification and cell cycle exit.**Conclusion** JAG1 facilitates cochlear prosensory cell cycle exit by upregulating p27 expression and depends on Notch1 and Notch2 receptor signaling for its pro-sensory functions.

Disclosures: R. Huang: None. **A. Doetzlhofer:** None.

Poster

PSTR228: Hair Cells and the Periphery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR228.11/AA30

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

Support: NIH Grant R01DC020209

Title: Female Gonadal Hormone Deficiency Attenuates Immune and Inflammatory Gene Responses to Acoustic Overstimulation in the Mouse Organ of Corti

Authors: *B. HU, M. YE;
Univ. of Texas at Dallas, Richardson, TX

Abstract: Sex differences in susceptibility to noise-induced hearing loss have been well documented, with females generally exhibiting greater resistance to acoustic injury than males. However, the molecular mechanisms underlying this sex-dependent protection remain poorly understood. We previously demonstrated that the expression of immune-related genes in the

cochlea varies across the estrous cycle in mice, suggesting that female gonadal hormones influence cochlear gene expression. Based on these findings, we asked whether changes in female gonadal hormone levels alter the molecular response of the organ of Corti (OC), the sensory epithelium that contains auditory hair cells and supporting cells, to acoustic overstimulation. Female mice underwent ovariectomy (OVX) to induce gonadal hormone deficiency. Mice were then exposed while awake to continuous broadband noise (1-7 kHz, 115 dB SPL re 20 μPa) for 2 hours to induce cochlear injury. Two days after exposure, OC tissues were collected for RNA sequencing (RNA-seq) analysis to characterize transcriptional responses to acoustic trauma. In control female mice, acoustic overstimulation induced significant upregulation of more than 350 genes in the OC. Bioinformatic analyses revealed that these genes were predominantly associated with immune and inflammatory processes, including innate immunity, immune responses, and complement activation. Acoustic overstimulation also elicited immune-related transcriptional responses in OVX mice. However, direct comparison of noise-induced gene expression changes between OVX and control mice identified numerous genes whose induction was significantly attenuated following ovariectomy. Functional enrichment analyses demonstrated that these attenuated genes were strongly associated with immune and inflammatory pathways. These findings indicate that loss of female gonadal hormones suppresses immune and inflammatory responses in the OC following acoustic injury, suggesting that female hormones contribute to the regulation of cochlear immune activity after noise exposure. This study provides new insights into the molecular basis of sex differences in cochlear responses to acoustic trauma and identifies hormone-dependent immune regulation as a potential mechanism underlying the enhanced resistance of females to noise-induced hearing loss.

Disclosures: B. Hu: None. **M. Ye:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.01/AA31

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant NS129112

Title: Comparison of frequency tuning and responsiveness in single-contact vs. multi-contact (Neuropixels) recordings in primary auditory cortex

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Abstract: The encoding of frequency in the auditory cortex is well-established and is a fundamental organizational principle of the auditory system[1-3]. However, the picture of frequency tuning at the individual neuron level is complex and remains contested, particularly

when considering different methods of evaluating tuning[4-6]. Most prior literature has relied on single-contact or low-density multi-contact electrophysiological recordings to establish tuning and responsiveness of individual neurons. The recent advent of the Neuropixels high-density multi-contact NHP long probe[7,8] offers an opportunity to revisit cortical frequency tuning and to compare with single-contact neural data collected under the same conditions. Such comparisons can investigate biases inherent to recording methodology that may influence subsequent scientific conclusions. In this study, we used single-contact tungsten electrodes in one macaque monkey and Neuropixels NHP silicon probes in two monkeys to record extracellular electrophysiology from the primary auditory cortex (A1). Monkeys sat passively in a dark, quiet room as randomly interleaved pure tones between 208-4076 Hz were played. Here, we present the preliminary findings from 75 single-contact-recorded neurons and 5 sessions of Neuropixels recordings that yielded several hundred neurons.Results suggest that single-contact-electrode neurons may preferentially capture highly responsive or broadly tuned neurons, due to the nature of listening for sound responsiveness when isolating units in recording. In contrast, Neuropixels probes, with hundreds of contacts distributed along the shank and no need for manual unit isolation, captures a wider range of neurons in terms of selectivity and responsiveness. Specifically, Neuropixels recordings included more cases of neurons that are finely-tuned (responsive to a small number of frequencies) than is typically the case for single-contact-electrode recordings. Across the entire frequency range, Neuropixels data also show lower percentages of neurons significantly responsive to each frequency, with the largest difference at lower frequencies. Single-contact data shows significantly higher levels of mean baseline firing rate overall. Importantly, however, when sound-evoked firing rates are z-scored to each neuron's individual baseline firing, the distributions of firing rates are the same between methods. Altogether, these results suggest that Neuropixels captures a broader population of neurons as compared to single-contact recording, and contribute to an overall picture of tuning in the auditory cortex that is preserved across methods.

Disclosures: J. Shih: None. **J.M. Leeman:** None. **A.S. Macklin:** None. **J.M. Groh:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.02/AA32

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC04290
NIH Grant GM109086

Title: Intracranial Investigation of Auditory Novelty Responses in a Roving Oddball Paradigm

Authors: *K. V. NOURSKI[1], M. STEINSCHNEIDER[2,1], M. LOU ANNE[1], A. E. RHONE[1], E. R. DAPPEN[1], M. I. BANKS[3];

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Abstract: Auditory roving oddball is a time-efficient paradigm to elicit novelty responses and is a valuable tool in studies of auditory processing, predictive coding, and consciousness research. The present study used intracranial electroencephalography (iEEG) to clarify the time course and regional distribution of adaptation and prediction error components of auditory roving oddball responses. Participants were neurosurgical patients undergoing invasive monitoring for identifying seizure foci. Stimuli were sequences of pure tones with pseudorandom changes in tone frequency (500-800 Hz). Recordings were made using depth electrodes in temporal, parietal and frontal lobe, including auditory cortex within the superior temporal plane and lateral superior temporal gyrus (STG). Data analysis focused on averaged evoked potentials (AEP) and power changes in canonical iEEG bands (alpha through high gamma). Novelty responses were examined as differences between responses to the first tone in a sequence (deviant) and those elicited following multiple presentations of the same tone (standard). High gamma novelty responses were primarily localized to superior temporal cortex whereas AEP and alpha and beta power changes had a broader distribution, including the frontal lobe and the insula. Novelty responses in the AEP contained two principal peaks, the first occurring between 75-150 ms, and the second at about 250 ms following stimulus onset. The first peak was maximal within caudal auditory cortical areas (core auditory cortex, planum temporale, posterior STG) and was earliest in core auditory cortex. The second peak was maximal within rostral areas (planum polare, anterior STG) and superior temporal sulcus (STS), with similar peak latencies across brain regions. The earlier AEP component dominated responses in the left posterior STG and STS, while the later component was more prominent in right STG and STS. The timing and distribution of AEP changes is consistent with dual mechanisms of novelty response, where the early and late peaks index neural adaptation and prediction error, respectively. These results provide a foundation for interpretation of impaired novelty responses seen in neuropsychiatric clinical populations and patients with disorders of consciousness.

Disclosures: K.V. Nourski: None. **M. Steinschneider:** None. **M. Lou Anne:** None. **A.E. Rhone:** None. **E.R. Dappen:** None. **M.I. Banks:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.03/BB1

Topic: E.05. Auditory and Vestibular Systems

Support: NEI R00 EY034546
Georgia Tech Smithgall-Watts Early Career Award
NEI R01 EY014645

Title: Auditory motion responses in the human planum temporale arise from independent spatial and temporal representations

Authors: ***Y. YANG**[1], K. H. CHANG[2], I. FINE[2], W. PARK[1];
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Abstract: The human planum temporale (PT) shows robust responses to auditory motion (Baumgart et al., 1999; Jiang et al., 2014; Warren et al., 2002). However, the representational basis of this response remains unclear (Battal et al., 2019; Smith et al., 2004, 2007). Specifically, it is unknown whether PT encodes auditory motion through genuine motion-sensitive mechanisms, analogous to visual motion processing, or by combining information about where and when sounds occur without dedicated motion detectors. Eleven neurotypical individuals (mean age = 29.18, SD = 7.28, 6 females) participated in an fMRI study examining auditory motion processing in PT. Stimuli consisted of nine broadband noise bursts (500-14000 Hz, 90 ms each) presented at different spatial locations over time, simulated via interaural time and level differences. Auditory motion coherence was manipulated. In the 100% coherence condition, the noise bursts sequentially moved either leftward or rightward. In the 50% coherence condition, the onset and offset of the stimulus (the first and last two bursts) were identical to the 100% condition whereas the middle segment was spatially shuffled. In the 0% coherence condition, the spatial locations of nine bursts were shuffled across time. PT was functionally identified in each hemisphere on the cortical surface using an independent auditory motion localizer. Univariate analyses revealed that PT responses decreased with increasing motion coherence, with stronger responses to shuffled (0%) than to fully coherent (100%) motion stimuli—a pattern consistent with independent representations of space and time. Representational similarity analysis showed that PT in the right hemisphere exhibited more distinctive multivariate response patterns across motion directions, with representational distances different from those predicted by motion-selective mechanisms. Finally, the best fitting vertex-wise encoding models consisted of independent tuning to temporal onset and offset at left and right spatial locations. These findings suggest that human PT represents auditory motion primarily through the combination of spatial and temporal signals rather than through dedicated motion-selective mechanisms analogous to those observed in vision. Auditory and visual motion processing may rely on fundamentally different representational strategies.

Disclosures: Y. Yang: None. **K.H. Chang:** None. **I. Fine:** None. **W. Park:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.04/BB2

Topic: E.05. Auditory and Vestibular Systems

Title: Tracing Internal Noise along the Auditory Pathway: From Peripheral Encoding to Brainstem and Perception

Authors: *M. ORF[1], T. SODENKAMP[3], J. OBLESER[2];
[1]Univ. of Luebeck, Lübeck, Germany; [2]Univ. of Luebeck, Luebeck, Germany; [3]Univ. of Lübeck, Lübeck, Germany

Abstract: Internal noise places fundamental limits on auditory perception. To investigate its origins and propagation across processing stages, we combined equivalent-noise analysis with computational modeling, neural recordings, and behavioral experiments. At the auditory periphery, clicks embedded in varying levels of external noise were simulated using the Zilany et al. (2014) model for healthy cochleae and simulated hearing loss (reduced outer hair cell function). Using a threshold-versus-noise (TvN) approach, we estimated elbow points (Nc) from auditory-nerve simulations at three neural SNR criteria. Reduced OHC function systematically increased Nc, indicating elevated effective internal noise, while reducing the divergence between TvN curves, consistent with a more linear cochlear response. As a proof of concept, Nc emerged as a sensitive marker of OHC dysfunction, whereas variability in Nc across TvN curves may provide a compact measure of cochlear nonlinearity. We next examined whether internal noise can also be quantified neurally by recording and modeling Auditory Brainstem Responses (ABRs) in a preliminary sample of four normal-hearing participants, with the final sample extending to 35. EEG was recorded while participants passively listened to Poisson-distributed click trains with independently varied click amplitude and external noise level. Increasing external noise systematically reduced temporal response function amplitudes and encoding accuracy, reflecting greater stimulus uncertainty. Using this framework, we estimated internal-noise thresholds directly from brainstem responses, demonstrating that early-stage internal noise can be quantified in humans. Finally, in a Two-Alternative Forced Choice detection task, the same listeners judged Poisson-distributed clicks embedded in Gaussian white noise while signal strength and external noise were independently manipulated. A simulation-tuned Bayesian adaptive procedure based on Lesmes et al. (2006), including a new Adaptive Parameter-Space Exploration approach (APEX), produced TvN estimates closely matching empirical 75% thresholds in an initial self-validation run. Across participants, distinct constellations of asymptotic noise-free signal threshold (N0) and internal-noise threshold (Nc) suggested separable perceptual profiles, with elevated Nc providing a behavioral analogue of the modeled effective internal-noise parameter. In sum, quantifying internal encoding noise is a promising approach for delineating individual differences in auditory processing difficulty.

Disclosures: M. Orf: None. **T. Sodenkamp:** None. **J. Obleser:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.05/BB3

Topic: E.05. Auditory and Vestibular Systems

Title: A Deep-Learning Framework for Linking Cochlear Bandwidth Constraints to Auditory Scene Analysis

Authors: *P. ATHUKORALA, A. NAIR, S. MISHRA;
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Abstract: Some listeners with clinically normal audiograms report difficulty understanding speech in complex acoustic environments, implying that clinical hearing tests fail to capture peripheral auditory mechanisms critical for real-world listening. Extended high frequency (EHF; >8 kHz) sensitivity indexes the fidelity of cochlear and auditory nerve encoding at the basal end of the tonotopic map, a region where high frequency spectral and temporal envelope cues supporting talker identity, spatial separation, and auditory stream segregation are first represented. We hypothesized that reduced EHF sensitivity constrains the quality of acoustic information delivered to central auditory circuits supporting binaural integration, stream segregation, and auditory scene analysis.
Behaviorally, young adults with normal audiograms but variable EHF thresholds completed a digit-in-noise task under four cue conditions: baseline (no informative cues), talker, spatial, and combined. Poorer EHF sensitivity selectively predicted elevated speech reception thresholds in talker, spatial, and combined cue conditions, but not in the baseline condition, consistent with EHF-dependent degradation of the peripheral representations that central circuits exploit for cue-based segregation.
To link these behavioral findings to computational mechanisms, we developed a deep-learning pipeline that models how frequency-limited cochlear representations affect downstream speech decoding. Target and masker utterances from the VCTK corpus were spatialized using CIPIC head-related transfer functions and mixed across multiple target-to-masker ratios. The resulting binaural signals were transformed into cochleagram representations approximating tonotopically organized peripheral auditory input. Full-bandwidth and low-pass variants (LP8, LP6, LP4 kHz cutoffs) simulated graded loss of high-frequency cochlear input. These binaural cochleagrams served as two-channel inputs to a CNN-BiLSTM-CTC phoneme decoder. The computational framework and deep-learning pipeline were implemented and validated, enabling evaluation of bandwidth constraints on cue-dependent speech recognition. Simulations across talker, spatial, bandwidth, and target-to-masker ratio conditions characterize how peripheral bandwidth restrictions propagate through the auditory processing hierarchy to impair cue-dependent speech recognition.
Collectively, these findings establish a mechanistic link between subclinical cochlear dysfunction at the extreme basal region and the degradation of central auditory computations that support speech understanding in noise.

Disclosures: P. Athukorala: None. **A. Nair:** None. **S. Mishra:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.06/BB4

Topic: E.05. Auditory and Vestibular Systems

Title: From EEG to spectrogram images: Using image generation models to reconstruct sound stimuli from EEG

Authors: J. LIM[1], *A. BURCH[1], I. CHOI[2];
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Abstract: Auditory neuroscience has long sought to reconstruct perceived acoustic stimuli from neural activity, but noninvasive electroencephalography (EEG)-based reconstruction remains limited by low spatial resolution, noise susceptibility, and weak recovery of detailed auditory structure. Although temporal response function (TRF)-based approaches show that EEG tracks speech features, reconstruction remains insufficient for high-fidelity stimulus recovery. Here, we investigated whether a conditional DDPM could provide a more detailed approach for reconstructing auditory spectrograms from EEG. We used an open-source Alice's Adventures in Wonderland EEG dataset of 49 subjects listening to chapter one of the audiobook. Audio was segmented into three target words: "Alice," "Her," and "That". They were then converted into 256 x 256 log-scaled STFT spectrograms, and corresponding EEG segments were preprocessed into 60 x 256 x 256 tensors. A CNN EEG encoder guided a conditional UNET during DDPM denoising. To test generalization, we used cross-validation where one known subject contributed 70% of EEG samples for training and 30% for testing, while one unseen subject was fully held out. Mean accuracy remained modest (known: r=0.159; unseen: r=0.145), indicating that the current model does not yet achieve reliable high-fidelity reconstruction across samples. However, best-case reconstruction reached r=0.59 for known-subject EEG and r=0.58 for alien-subject EEG, suggesting that the model can sometimes recover substantial spectrotemporal structure. To test whether low mean performance reflected DDPM failure or a conditioning bottleneck, we compared performance with chance baselines. Mean similarity exceeded chance in both conditions, providing evidence that EEG conditioning contributed information to denoising. We then visualized EEG embeddings using t-SNE and observed poor separation among word classes, suggesting that the CNN encoder did not reliably organize EEG representations by stimulus identity. These analyses suggest that the conditional DDPM framework is capable of EEG-guided spectrogram generation, but reconstruction fidelity is limited by weak discriminative structure in the encoder. Future work will pretrain a stronger EEG encoder inspired by established EEG-CNN architectures before DDPM integration. Overall, this study supports EEG-conditioned diffusion models as a promising direction for noninvasive auditory stimulus reconstruction, with potential relevance for neural decoding, cognitive monitoring, and brain-computer communication.

Disclosures: J. Lim: None. **A. Burch:** None. **I. Choi:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.07/BB5

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC012947
NIH R01DC019979
NIH R01MH134118-01

Title: Circuit modeling of schizophrenia-related 40 Hz auditory steady-state response deficits constrained by primate LFP/CSD and MEG data

Authors: *S. MCELROY[1], S. A. NEYMOTIN[2], S. DURA-BERNAL[3];
[1]SUNY Downstate Med. Ctr., Ridgewood, NY; [2]Nathan Kline Inst., Orangeburg, NY; [3]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

Abstract: Reduced 40 Hz auditory steady-state response (ASSR) power is a robust electrophysiological phenotype in schizophrenia, but the cell-type-specific circuit mechanisms linking molecular pathology to electro- and magnetoencephalography (EEG/MEG) abnormalities remain unclear. To investigate these mechanisms, we extended our previously developed multiscale model of auditory thalamocortical circuits. The model simulates a cortical column with more than 12,000 neurons and 30 million synapses, with cell densities, laminar distributions, biophysical properties, and long-range, local, and dendrite-specific connectivity constrained by published experimental data. Under control conditions, the model reproduced cell-type- and layer-specific firing rates, local field potentials (LFPs), EEG/MEG responses, and healthy 40 Hz ASSR dynamics.To improve model fitting to human auditory electrophysiology, we implemented a parameter optimization strategy to reproduce laminar LFP and current source density (CSD) data from primate cortical recordings. Because many parameter sets can reproduce firing rates or oscillatory power while producing different transmembrane current patterns, CSD provides a more direct constraint on the transmembrane current sinks and sources that shape EEG and MEG signals. By quantifying laminar CSD profiles, we optimized synaptic locations, delays, and strengths to identify parameter combinations that generate the most accurate auditory response dynamics. This approach prioritizes parameters more directly linked to macroscopic field generation than firing rates or oscillatory power alone.Beyond our improved parameter optimization approach, we are including MEG data that uses optically pumped magnetometers (OPM). OPM-MEG offers wearable, closer-to-scalp magnetic recordings that can improve comfort and enhance signal to noise ratio. Collaborator Peter Uhlhaas has provided OPM-MEG data from schizophrenia patients which has significantly improved the specificity of our validation. These recordings provide additional constraints on the timing and spatial origin of auditory responses, including potential thalamocortical contributions. With the use of tools such as LFPyKit we have been able to extend our model to simulate realistic MEG signals. Together, CSD-based optimization and OPM-MEG validation improved the model's ability to reproduce auditory-evoked responses across scales and recording modalities. This multimodal framework provides a more biologically constrained platform for identifying how cell-type-specific circuit alterations reduce 40 Hz ASSR power in schizophrenia.

Disclosures: S. McElroy: None. **S.A. Neymotin:** None. **S. Dura-Bernal:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.08/BB6

Topic: E.05. Auditory and Vestibular Systems

Support: University of Minnesota CLA Social Sciences Research Grant
University of Minnesota SLHS Graduate Student Summer Fellowship

Title: Perception and subcortical encoding of audiobooks presented in different types and levels of noise

Authors: *I. N. HERB, M. R. TORTOMASI, M. J. POLONENKO;
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Abstract: Our ability to understand speech in different listening scenarios varies based on the type of noise we encounter. While these perceptual effects of noise masking have been well studied, the subcortical neural encoding has been less so. Recent work enabled the measurement of auditory brainstem responses (ABRs) to continuous speech, which has shown systematic changes with decreasing signal-to-noise ratio (SNR) with multiple talkers. In this study we extended this work to assess both perceptual and ABR responses to speech in quiet and in the presence of different types of noise maskers presented at the same SNRs of 0 and +3 dB. These conditions were chosen to range from informational masking (interference from competing speech from 2- and 4-talker babble) to energetic masking (spectral overlap with the target signal from 12-talker babble and speech-weighted noise). We recruited 26 adults aged 18-29 years (21 female, 3 male, 2 non-binary) with normal hearing (≤20 dB HL from 250-8000 Hz). Participants completed a coordinate response measure task by identifying the color and number spoken by a male target amid the different noise conditions using an adaptive threshold procedure. The babble maskers consisted of audiobooks narrated by different male talkers. Afterwards, 2-channel ABRs were recorded during passive listening to one target male-narrated audiobook in quiet and in the same noise conditions as the perceptual task (10 min/condition interleaved randomly every 20s). Outcomes included perceptual dB SNR thresholds and ABR wave V peak amplitudes and latencies, which were normalized as proportional change from the quiet condition. Conditions were compared using linear mixed effects models. As expected, perceptual thresholds were best (i.e., lowest dB SNR) for the maskers where listening could occur in the gaps between words (2- and 4-talker babble). But interestingly, thresholds were better for SWN than for 12-talker babble. ABR amplitudes also systematically decreased from 2-talker to 12-talker babble and further decreased for SWN, despite the same masker SNR. Worsening the masker SNR from +3 to 0 dB SNR slightly decreased wave V amplitude further. ABR wave V latency did not significantly change across conditions. Overall, these results reveal that as masking becomes more energetic, perception and subcortical encoding of continuous speech becomes more degraded. Future analyses will investigate correlations between the behavior and neural measures. Characterizing the different stages of auditory processing in young, normal hearing adults lays the foundation that is helpful for extending this work to other populations with known speech and noise difficulties.

Disclosures: I.N. Herb: None. **M.R. Tortomasi:** None. **M.J. Polonenko:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.09/BB7

Topic: E.05. Auditory and Vestibular Systems

Support: R21DC018327784
R01DC020459

Title: Noise-modulated cortical subnetworks form a circuit for noise-invariant hearing

Authors: *T. SUAREZ OMEDAS[1], R. S. WILLIAMSON[2];
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Abstract: A fundamental challenge of the auditory system is accurately representing sounds in the presence of background noise (BN). Foundational work has shown that sound representations become progressively more noise-invariant both along the ascending auditory hierarchy, from the periphery to auditory cortex (ACtx), and within ACtx across layers (L) 2/3 and L5. However, the specific mechanisms by which ACtx neurons receive noise-dependent inputs and propagate noise-invariant representations remain poorly understood. Holographic optogenetics is an emerging approach in systems neuroscience that probes functional connectivity by photostimulating small, targeted neuronal ensembles and quantifying their influence on neighboring non-stimulated neurons. Here, we leverage this approach to test whether ACtx neurons organize into functional subnetworks defined by shared modulation by BN. We co-expressed GCaMP8s and the red-shifted opsin ChrimsonR in L2/3 of mouse ACtx, enabling simultaneous calcium imaging and targeted optogenetic stimulation. Using two-photon calcium imaging, we first mapped the functional properties of L2/3 neurons in response to pure tones presented without noise (No-BN) and with continuous 50 dB SPL white noise (BN). For each neuron, we identified two properties: its best frequency and its modulation motif, defined as the direction of response modulation (enhancement or suppression) to the same pure tones in BN. Returning to the same field of view, we then performed holographic optogenetics experiments in which we photostimulated local ensembles of 5-7 neurons that either shared the same modulation motif (co-modulated) or the same best frequency (co-tuned), and measured the influence of this stimulation on non-stimulated neurons. Photostimulated co-modulated ensembles preferentially influenced non-stimulated neurons with a matching modulation motif over those with a different one. These results show that ACtx neurons organize into noise-modulated subnetworks, providing a circuit substrate for the emergence of noise-invariant sound representations in ACtx.

Disclosures: T. Suarez Omedas: None. **R.S. Williamson:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.10/BB8

Topic: E.05. Auditory and Vestibular Systems

Support: R01 DC020459, NIH/NIDCD
Klingenstein-Simons Fellowship Award in Neuroscience
F31 DC021867, NIH/NIDCD

Title: Arousal-dependent modulation of perceptual decision-making in auditory cortex

Authors: *K. KAUFMAN[1], N. A. SCHNEIDER[2], R. S. WILLIAMSON[2];
[2]Otolaryngology, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Arousal state, indexed by pupil diameter, varies continuously and shapes cortical activity and sensory processing. Auditory cortex (ACtx) is a critical hub for acoustic processing and contains diverse excitatory neuron populations spanning cortical laminae, including intratelencephalic (IT) and extratelencephalic (ET) neurons. These subpopulations differ in their connectivity, intrinsic properties, and state-dependent activity patterns. Recent work showed that increases in arousal enhanced neural activity, reliability, and sound encoding in L5 ET neurons during passive listening, whereas L5 IT neurons were unaffected and L2/3 IT neurons exhibited an inverted-U trend (Kaufman et al., 2026). However, it remains unknown whether these cell-type-specific effects persist, or are reorganized, when sounds become behaviorally relevant during active listening. To address this, we determine how pupil-linked arousal influences IT and ET neurons across active and passive listening. Head-fixed mice were trained on a two-alternative choice task where they categorized the modulation rate of sinusoidally amplitude-modulated (sAM) noise as “fast” or “slow”, reporting their choice by licking one of two spouts (Schneider et al., 2025). Face videography and two-photon calcium imaging simultaneously captured pupil diameter and the activity of thousands of ACtx neurons, recorded across both active and passive listening contexts. We first asked whether listening context altered pupil-linked arousal. Baseline pupil size was skewed toward higher-arousal states during passive listening but varied more during active listening. In contrast, stimulus-evoked pupil responses were larger during active than passive listening. These effects were independent of the order in which mice experienced each context, indicating that arousal is systematically reconfigured when sounds become behaviorally relevant. Because trial-to-trial fluctuations in behavioral state can influence perceptual decision-making, we next applied a Generalized Linear Model-Hidden Markov Model (GLM-HMM) framework to identify discrete latent performance states. This revealed distinct “optimal” and “biased” latent states that differ in stimulus sensitivity and choice strategy and are not apparent from overall task performance alone. By aligning these latent states and arousal with neural activity, ongoing analyses test how internal-state fluctuations shape sound encoding within IT and ET populations during active and passive listening. Collectively, this work will clarify how arousal and behavioral context jointly shape cell-type-specific sensory representations in ACtx.

Disclosures: K. Kaufman: None. **N.A. Schneider:** None. **R.S. Williamson:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.11/BB9

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC015527
NIH R01DC014479
NIH R01NS113241

Title: Neuronal correlates underlying auditory categorization in mice

Authors: *A. SINHA[1], M. N. GEFFEN[2], Y. E. COHEN[3];
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Abstract: Categorization of sensory stimuli is a fundamental computation in cognition, and is critical for many aspects of learning, perception, and prediction. Auditory categorization has been linked to the neuronal activity in the auditory cortex (AC), however, it remains poorly understood how categorical representations emerge in population neuronal activity with learning. To understand neuronal correlates of auditory categorization, we recorded activity from AC and anterior cingulate cortex (ACC) of mice implanted with Neuropixel electrodes while training them to perform auditory categorization task using 2-alternative forced choice task. We used a variant of a task that we have previously designed that allowed to isolate specific "hidden" variables in behavior, such as perseveration and behavioral bias (Collina et al., 2025).
We examined neuronal responses to sound and to behavioral stimuli over the course of learning. Approximately 30% of the recorded neurons in AC exhibited category preference. The accuracy of decoding of categories by AC neuronal population increased with learning. As expected, learning increased alignment between neurometric and psychometric thresholds, suggesting that neuronal activity reflected behavioral performance. Moreover, a subpopulation of neurons in AC was choice-selective, as their firing rate reflected the choice of the mouse across trials. Additionally, we also identified components in the population responses that signaled reward prediction and reward response in AC. Initially, neuronal population in ACC did not respond to sound. However, with learning, sound representations emerged in ACC and neuronal population exhibited category selectivity. Interestingly, choice selective responses became more stimulus-locked in ACC with learning.
We thus find that neuronal activity in the AC during categorization reflects behavioral performance, and sound responses emerge in ACC with learning. Combined, our data suggests that as behaviorally relevant representations emerge in sensory regions, sensory representations become stronger in higher order cortical regions.

Disclosures: A. Sinha: None. **M.N. Geffen:** None. **Y.E. Cohen:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.12/BB10

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC015527
NIH R01DC014479
NIH R01NS113241
NIH F31DC022507

Title: Somatostatin-positive interneurons drive contrast gain control in the mouse primary auditory cortex

Authors: *O. ZELIGER[1], C. F. ANGELONI[3], M. N. GEFFEN[2];
[2]Otorhinolaryngology, [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Dept. of Neurobio., Northwestern Univ., Evanston, IL

Abstract: In natural environments, behaviorally-relevant sounds such as speech often co-occur with background noise such as wind or traffic. In order to effectively identify and respond to relevant sounds, the auditory system must isolate signal from noise. One strategy for isolating signal from noise is to adapt to the statistics of the current auditory environment. In the primary auditory cortex (**A1**), neurons adapt to changes in stimulus variability (**contrast**) by adjusting their gain. This process is known as contrast gain control (**CGC**). Though CGC has been demonstrated across many organisms from mice to humans, its mechanisms are still unknown. In this study, I test the hypothesis that two different classes of inhibitory interneurons, parvalbumin (**PV**)- and somatostatin (**SST**)-positive interneurons, drive contrast gain control in mouse A1.
In order to test the role of different inhibitory interneuron subtypes in driving CGC, we optogenetically suppressed PV or SST populations in A1 of mice presented with stimuli of changing contrasts. We tested for CGC using two methods: behavioral performance on a target-detection task, and extracellular electrophysiological recordings in A1.
First, we tested how optogenetically suppressing different populations of interneurons affected behavioral performance on a target-detection task. Mice were presented with stimuli of low and high contrasts and trained to respond when they detect an increase in sound pressure level. Previous experiments in mice and humans show that performance on similar tasks increases in low-contrast backgrounds, corresponding to increased neuronal gain. If PV or SST neurons drive CGC, we expect optogenetic suppression of these populations to reduce the change in performance between the two contrasts. We found that SST suppression, but not PV suppression, impairs CGC between high and low contrast conditions. Second, we performed acute extracellular recordings in mice passively exposed to auditory stimuli with high and low contrasts. Using these neuronal responses, we directly calculated neuronal gain changes across stimulus contrasts. If PV or SST neurons drive CGC, we expect optogenetic suppression to reduce the degree of gain adaptation between the two contrasts. Similar to the behavioral results,

we observed that SST but not PV suppression significantly decreased the degree of contrast gain control.
Together, these results suggest that SST-positive interneurons drive CGC in mouse A1. By characterizing the neural mechanisms of contrast adaptation, this study establishes the role of local inhibition in the auditory system allowing hearing in noisy environments.

Disclosures: O. Zeliger: None. **C.F. Angeloni:** None. **M.N. Geffen:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.13/BB11

Topic: E.05. Auditory and Vestibular Systems

Support: SFARI Pilot award

Title: Distinct autism-associated mutations produce convergent and divergent changes in auditory processing

Authors: M. AIZENBERG[1], S. ROGERS[1], A. SINHA[1], ***M. N. GEFFEN**[2];
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Abstract: Autism spectrum disorder (ASD) is commonly associated with deficits in sensory processing, including hypo- and hyper-auditory sensitivity, reduced adaptation to predictable sounds and impaired detection of unexpected sounds. The genetic causes for ASD are highly heterogenous, and it remains unclear how distinct risk mutations affect auditory cortical circuits and processing. Here, we combine in-vivo electrophysiology with cell-type-specific anatomical analysis to identify shared and mutation-specific alterations in auditory cortical processing in two clinically relevant mouse model of ASD: *16p11.2* del/+ and *Nrxn1α* del/+ heterozygous deletion. We first confirmed that mice from *16p11.2* del/+ and *Nrxn1α* del/+ strains exhibit normal hearing using auditory brainstem responses (ABR). Next, we recorded neuronal activity using high-density Neuropixel recordings in the primary auditory cortex (A1) of awake head-fixed mice presented with auditory stimuli. We find that neurons in primary auditory cortex (A1) from *16p11.2* del/+ and *Nrxn1α* del/+ mice exhibit increased frequency selectivity compared to their wildtype littermates. In contrast, stimulus-specific adaptation (SSA), a neuronal signature of auditory prediction and novelty detection, is differentially affected across the ASD models. A1 neurons in *16p11.2* del/+ mice show reduced SSA, driven by decreased responses to unexpected sounds (prediction error), whereas neurons in *Nrxn1α* del/+ mice exhibit enhanced SSA driven primarily by increased adaptation to repeated sounds (repetition suppression).
Our previous studies show that distinct types of inhibitory cortical interneurons play a critical function in controlling frequency discrimination and SSA: parvalbumin-positive (PV) interneurons regulate frequency selectivity in A1, whereas somatostatin-positive (SST) interneurons regulate SSA. To link these functional phenotypes of underlying circuit

organization, we performed RNAscope and immunohistochemistry to quantify the density of major inhibitory interneuron classes in A1. Preliminary analyses reveal mutation-specific differences in PV and SST neuronal density.
Together, these findings indicate that distinct ASD-associated genetic mutations converge on increased auditory sensitivity while diverging in cortical adaptation through differential impacts on inhibitory circuit composition. Our work provides a circuit-level framework for understanding heterogeneity in auditory sensory phenotypes in ASD and supports our hypothesis that ASD-associated genetic mutations affect excitatory-inhibitory cortical microcircuits, which result in sensory dysfunction.

Disclosures: M. Aizenberg: None. **S. Rogers:** None. **A. Sinha:** None. **M.N. Geffen:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.14/BB12

Topic: E.05. Auditory and Vestibular Systems

Title: Distinct alterations in hierarchical auditory predictive processing in mouse models of autism and modulation by psychedelics

Authors: *S. A. ROGERS[1], M. AIZENBERG[1], A. SINHA[2], M. N. GEFFEN[3];
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Abstract: Hyper- and hypo-responsiveness to auditory stimuli are among the most prevalent sensory disturbances in autism spectrum disorder (ASD). Individuals with ASD commonly exhibit more complex forms of auditory predictive processing dysfunction, including delayed and reduced mismatch negativity signals. Predictive processing theories propose that these deficits may arise from altered neural representations of environmental regularities, yet the circuit mechanisms underlying divergent predictive processing deficits in ASD remain unclear. To tease apart the potential contributions of distinct inhibitory interneurons, we tested how hierarchical predictive coding is affected in two common genetic mouse models of ASD, *Nrxn1α* del/+ and *16p11.2* del/+ models. We performed acute Neuropixels recordings in the primary auditory cortex (A1) of awake head-fixed mice during presentation of an auditory pattern-violation paradigm. Two repeating tone sequences (AAAB and CCCD) established local and global regularities, while infrequent violations (AAAD and CCCB) generated locally and globally deviant stimuli. Responses were compared to many-standard and cascade control stimuli to quantify repetition suppression (RS), local prediction error (PE), and global prediction error (PE). We assessed population discriminability between deviants using a Fisher information decoder. In the pattern-violation paradigm, A1 neurons from *Nrxn1α* del/- mice displayed enhanced local PE responses, but markedly reduced global PE responses, resulting in a bias toward local deviance detection. Population decoders more frequently confused local and global deviants in populations of A1 neurons from *Nrxn1α* del/+ mice than from their wild-type

littermates. These results suggest that predictive auditory computations dependent on cortical microcircuits are systematically impaired in ASD models in a manner indicating specific dysfunctions of cortical interneurons. Currently, we are testing *16p11.2* del/+ mice in this paradigm and aim to pharmacologically manipulate these circuits with the psychedelic compound psilocybin, which can precisely tune cortical microcircuits. This project will elucidate cortical circuit differences underlying predictive processing deficits across ASD models.

Disclosures: S.A. Rogers: None. **M. Aizenberg:** None. **A. Sinha:** None. **M.N. Geffen:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.15/BB13

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 DC014950

Title: Cell type specific organization of sound feature encoding in auditory cortex

Authors: *S. V. DAVID[1], H. K. SRIVASTAVA[2], M. GHIMIRE[4], C. G. SWEENEY[6], A. E. TAKESIAN[7], R. S. WILLIAMSON[5], M. J. MCGINLEY[3];
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Abstract: Cortical neurons can be distinguished by gene expression, morphology, and patterns of connectivity. Prior work in auditory cortex (AC) and other sensory areas have reported differences in sensory coding properties between these neural populations, but results have sometimes been ambiguous and even conflicting. We hypothesize that differences between defined cortical populations have been obscured by two major factors. First, the precision with which neural populations are defined has been limited. Second, sensory coding properties have been characterized with relatively small sets of synthetic stimuli, limiting the granularity of functional characterization.
To address these limitations, we used viral strategies to target distinct populations of neurons in mouse AC for two-photon imaging, based on gene expression and projection patterns. We also optimized a set of nearly one million distinct natural sounds to probe neural auditory encoding. Experiments targeted populations of layer 1 inhibitory (L1), layer 2/3 pyramidal (L2/3), layer 5 intratelencephalic (IT) and layer 5 extratelencephalic neurons.
Spectrotemporal receptive field (STRF) models developed previously for characterizing sound encoding from neural spiking activity were adapted to measure encoding properties in two-photon data, after deconvolution to extract putative spiking events. Tuning properties measured from STRFs revealed topographic organization of multiple tuning properties, including best

frequency, spectral modulation, and temporal modulation tuning. While topography existed, there was substantial variability among neighboring cells, consistent with a salt and pepper organization. The average strength and spatial extent of topography varied between neural populations, strongest for L2/3 and weakest for L1 neurons.
The specific tuning properties driving topographic organization varied substantially between fields of view. However, STRF models were consistently able to reproduce the magnitude and spatial extent of signal correlation between pairs of neurons and to reproduce the different patterns of topography between neural populations. In summary, we have shown that encoding model analysis can describe tuning of two-photon signals for spectrotemporal sound features. These models capture sound feature tuning that defines the topographic organization of AC and provide a tool for understanding how sensory information is transformed as it passes through the cortical circuit.

Disclosures: S.V. David: None. **H.K. Srivastava:** None. **M. Ghimire:** None. **C.G. Sweeney:** None. **A.E. Takesian:** None. **R.S. Williamson:** None. **M.J. McGinley:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.16/BB14

Topic: E.05. Auditory and Vestibular Systems

Support: NIH BRAIN Initiative Grant R01NS131993

Title: Divergent communication subspaces from primary auditory cortex to dorsal and ventral streams support functional specialization

Authors: *M. B. NARDOCI[1], Z. TOMLINSON[2], W. GILLESPIE[3], J. EDDY[4], S. JARAMILLO[1], J. M. MURRAY[1];
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Abstract: Sensory processing in the auditory cortex relies on coordinated communication across a network of primary and non-primary cortical areas. However, the precise information transmitted across these interconnected cortical pathways remains unknown. To investigate the functional communication between auditory cortical regions, we recorded neural population activity simultaneously across primary and non-primary auditory areas of head-fixed mice, while presenting ensembles of sounds that included pure tones, amplitude-modulated (AM) white noise, and natural sounds. We first evaluated how well stimulus identity could be decoded from neural population activity and found that the primary auditory area achieved the highest decoding accuracy across all sound categories. Among non-primary regions, the ventral area outperformed the dorsal area specifically for natural sounds and AM white noise. We then evaluated inter-areal communication using canonical correlation analysis (CCA), a method that

identifies shared low-dimensional patterns of activity between neural populations. The latent communication subspaces from the primary area to the dorsal and ventral regions were significantly more orthogonal than expected by chance, demonstrating that distinct acoustic information is conveyed to each downstream target. This divergence in information flow likely underlies the distinct computational roles of the dorsal and ventral auditory streams.

Disclosures: M.B. Nardoci: None. **Z. Tomlinson:** None. **W. Gillespie:** None. **J. Eddy:** None. **S. Jaramillo:** None. **J.M. Murray:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.17/BB15

Topic: E.05. Auditory and Vestibular Systems

Support: R01 DC020459 (NIH/NIDCD)
Klingenstein-Simons Fellowship Award in Neuroscience
T32-NS126122 (NIH)

Title: Distributed top-down control of auditory cortex

Authors: *M. MALINA[1], R. S. WILLIAMSON[2];
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Abstract: Perception is an active process in which behavioral goals, environmental context, and internal state dynamically modulate primary sensory cortices. Top-down corticocortical feedback is a key mechanism underlying this modulation, and prior studies have shown that individual feedback projections can shape sensory processing and influence behavior. Primary auditory cortex (ACtx) receives feedback from multiple higher-order cortical areas, including premotor, motor, and association cortex, and its responses vary markedly with behavioral context. To dissect the functional contributions of distinct feedback sources, we developed a clear-skull preparation enabling temporally precise, unilateral optogenetic inactivation of numerous areas tiling dorsal cortex within a single recording session. We recorded ~750 single units across eight awake PV-Ai32 mice during passive presentation of amplitude-modulated pure tones. On randomly interleaved trials, we inactivated one of nine cortical targets to assess the contribution of distinct feedback sources to single-unit firing and stimulus tuning.
These inactivations bidirectionally modulated auditory cortical firing rates along an anterior-posterior (AP) gradient: inactivating anterior (prefrontal) regions most strongly increased firing, whereas inactivating the most posterior (association) regions weakly decreased it. This modulation was significantly greater in PV-Ai32 mice than in light-only C57 controls. Unsupervised clustering of response profiles revealed three subpopulations defined by which regions most strongly modulated their firing: those dominated by anterior feedback, those

dominated by posterior feedback, and those without a clear regional preference. Neurons most sensitive to anterior feedback had greater stimulus-driven responsiveness and were enriched for fast-spiking interneurons, which exhibited three-fold steeper AP gradients than regular-spiking neurons. Changes in ACtx firing rates varied systematically with the AP coordinate of the inactivation region, a dependence that captured significantly more variance in PV-Ai32 mice than in shuffled controls or matched-population C57 controls. Population-level representational dissimilarity matrices for the stimuli were indistinguishable across inactivation conditions, indicating that the AP gradient affects both spontaneous and evoked firing rates but not tuning-curve shape. These findings demonstrate that passive cortical feedback modulates auditory cortex through a spatially graded gain signal that uniformly scales neural responses without reshaping stimulus tuning.

Disclosures: M. Malina: None. **R.S. Williamson:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.18/BB16

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC022676
NIH Grant DC012557

Title: Developmental and environmental factors shape single-cell and population dynamics in the postnatal mouse auditory cortex

Authors: *M. M. VAZE[1], M. A. KIRCHGESSNER[2], R. C. FROEMKE[3];
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Abstract: Altricial animals like mice are born with immature sensory systems and are suddenly exposed to a rich acoustic environment upon hearing onset around postnatal day (P)12. How does the auditory cortex initially process sensory inputs, and how does this change with experience? To address this, we have performed longitudinal two-photon calcium imaging of the auditory cortex in young mice (N=31) in response to pure tones (4-64 kHz) and pup ultrasonic vocalization (USV) playbacks from hearing onset and, in 21/31 animals, into adulthood (P42-72). By tracking individual excitatory and inhibitory neurons across recording days (Majnik et al. 2025), we have observed varied degrees of stability and drift in tuning to different tone frequencies, with inhibitory neurons showing pronounced tuning shifts, especially towards higher frequencies in the first week of hearing. Although excitatory neurons exhibit greater tone encoding and population-level stability, Tensor Component Analysis (Williams et al. 2018) has revealed organized, subpopulation-level tuning changes underlying tonotopic maturation in the auditory cortex. These changes can be biased by acoustic experience such that five days of

repeated tone exposure during the critical period for tonotopic reorganization (Zhang et al. 2001, Villers-Sidani et al. 2007) shifts individual excitatory neurons' tuning towards the exposed tone frequency (n=171 cells in N=3 animals, P13 vs. P17: $p<0.001$), whereas inhibitory cells exhibit more dynamic changes.
We have also observed that the emergence of high-frequency tuning is delayed (P15-20) relative to lower frequencies (P12-14) and coincides with the onset of USV-evoked activity. Many early USV responses are observed in high-frequency tuned cells, some of which retain USV responsivity even as their frequency tuning shifts. Initially high correlations between high-frequency tone and USV responses diminish into adolescence and frequency tuning becomes less predictive of their USV responsivity, suggesting that representations of vocalizations become more complex. To relate these changes to the animals' experience, we have recorded USVs in pups' home cages (N=4 litters of n=6-10 pups, 3/4 with concurrently imaged pups). Although separated and/or isolated pups cease vocalizing around P16 (Pranic et al. 2025), we have recorded 177 USVs/hour on average between P17-26, demonstrating that mice naturally experience USVs when the auditory cortex is sensitive to ultrasonic sounds but is still maturing and plastic. Overall, our results reveal how cellular, developmental, and environmental factors influence sensory representations in the postnatal auditory cortex.

Disclosures: M.M. Vaze: None. **M.A. Kirchgessner:** None. **R.C. Froemke:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.19/BB17

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC017785
NSF ECCS2032649
NSF OISE2020624
NIH U19NS107464

Title: Patchy intra- and inter-layer hexagonal grid-like networks in mouse auditory cortex enable discrete tone integration

Authors: M. WANG[1,2], ***S. MUKHERJEE**[3,4,5], S. KHOSRAVI[4,5], P. JENDRICHOVSKY[1,2], J. DAHER[1,2], B. TASIC[6], T. L. DAIGLE[6], B. BABADI[4,5], P. O. KANOLD[1,2];
[1]Dept. of Biomed. Engin., [2]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD; [3]Northwestern Univ., Chicago, IL; [4]Dept. of Electrical and Computer Engin., [5]Inst. for Systems Res., Univ. of Maryland, College Park, MD; [6]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Sensory cortical neurons are organized in interconnected layers. While anatomical studies can reveal neuronal circuits, the crucial remaining gap is to link functional connectivity with functional properties. Here, we develop an all-optical *in vivo* approach that combines 2-

photon imaging, holographic optogenetic stimulation, network inference, and statistical connectivity modeling for causal mapping of functional connections across layers. To better understand the connectivity in the ascending cortical sensory processing pathway, we simultaneously imaged layer 4 (L4) and layer 2/3 (L2/3) neurons of the mouse auditory cortex (ACtx) while delivering optogenetic activation of small subsets of neurons at the single-neuron level precision in either layer as a perturbation strategy to causally probe interlaminar functional connectivity. We mapped the connectivity of excitatory neurons (Ai203; Vglut1-Cre; $Cdh23^{Ahl/ahl}$) and found that, in ACtx, functionally connected neurons in L4 and L2/3 exhibited both local and distal connectivity that varied with neuronal tuning relationships and cortical position in a hexagonal pattern with a spacing reflecting octave relationships. Interlaminar connections were mainly columnar and depended on the tonotopic axis. The existence of discrete patchy connections in ACtx defines a hexagonal circuit motif that could support the integration of discrete harmonic frequency components.

Disclosures: M. Wang: None. **S. Mukherjee:** None. **S. khosravi:** None. **P. Jendrichovsky:** None. **J. Daher:** None. **B. Tasic:** None. **T.L. Daigle:** None. **B. Babadi:** None. **P.O. Kanold:** None.

Poster

PSTR229: Neural Coding in the Auditory System

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR229.20/BB18

Topic: E.05. Auditory and Vestibular Systems

Support: National Science Foundation Graduate Research Fellowship Program (NSF-GRFP)

Title: Nuclear Factor I transcription factors in cochlear development

Authors: *R. N. D. DONGMO[1], C. MORGAN[2], R. HUANG[2], A. DOETZLHOFER[2]; [1]Neurosci., Johns Hopkins Univ., Baltimore, MD; [2]Neurosci., Johns Hopkins University, Sch. of Med., Baltimore, MD

Abstract: The objective of this study is to define the distinct roles of nuclear factor one (NFI) transcription factors in auditory sensory differentiation and supporting cell maturation, with the goal of informing strategies for hair cell regeneration in the mammalian cochlea. Hair cell (HC) loss accounts for the majority of hearing impairment currently affecting millions of Americans. Supporting cells (SCs) in non-mammalian vertebrates can regenerate hair cells (HCs) through mitotic and non-mitotic mechanisms. This regenerative competence is lost in mammals once cochlear SCs undergo maturation, which in rodents occurs shortly after birth. The identity of these restrictive signals and the molecular mechanisms driving cochlear SC maturation remain an active area of research. NFI transcription factors are likely candidates due to their ability to suppress cell proliferation while promoting differentiation. For instance, in the developing

cortex, loss of NFIA, NFIB, and NFIX (NFIA/B/X), disrupts or delays the differentiation of neuronal and glial cell types. Informed by these previous findings, we hypothesize that NFI transcription factors regulate cochlear supporting cell differentiation and maturation. Employing single cell RNA-sequencing datasets and cryosection immunofluorescence, we reveal that NFIA and NFIB are expressed in cochlear HC and SC progenitors at E14.5 prior to cellular differentiation. SOX2-CreERT2 mediated conditional deletion of Nfia, Nfib, and Nfix in cochlear progenitors at E12.5, the onset of cell cycle exit, results in delayed terminal mitosis and differentiation of both HCs and SCs in NFIA/B/X knockout mutants (NFI TKO). To restrict Nfia, Nfib, and Nfix deletion to the sensory epithelium of the cochlea, we bred NFIA/B/X floxed mice to Tecta-Cre mice. Bulk RNA-sequencing analysis reveal that deleting NFI transcription factors causes upregulation of genes promoting cell proliferation and stem cell renewal, as well as markers implicated in the cell cycle and DNA replication, including Hmga2, Lin28b, and Mki67. This persistent proliferation in the absence of NFI factors is further corroborated by immunofluorescence analysis showing elevated Ki67 protein expression in Tecta-Cre and NFI TKO mutants shortly after birth. NFI TKO mutants also exhibit progressive HC loss and cochlear degeneration beginning around hearing onset in a basal-to-apical gradient and deafness in adulthood. Our findings implicate NFI factors as regulators of cochlear differentiation and maturation. Understanding the mechanisms driving their transcriptional control will inform novel strategies to restore auditory function.

Disclosures: R.N.D. Dongmo: None. **C. Morgan:** None. **R. Huang:** None. **A. Doetzlhofer:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.01/BB19

Topic: E.06. Vision

Support: NIH Grant R01EB029813
NIH Grant R01NS122742
NIH Grant U24NS124001
NIH Grant U01MH130907

Title: Cell-type- and layer-specific mechanisms of visually induced oscillations in a bio-realistic mouse V1 model

Authors: *B. HERRERA, S. ITO, D. HAUFLER, K. DAI, A. ARKHIPOV;
Allen Inst., Seattle, WA

Abstract: Recent experimental studies have suggested the existence of a robust spectro-laminar (SL) motif for cortical oscillations, in which gamma oscillations (30-100 Hz) are prevalent in granular layers and alpha/beta oscillations (8-30 Hz) in deep layers. Prevalence and properties of

this SL motif are debated, and the underlying circuit mechanisms are poorly understood. We used a bio-realistic large-scale model of mouse primary visual cortex (V1; ~66,000 neurons, 21 cell classes across layers L1-L6; Ito et al., 2026) to investigate cell-type- and layer-specific mechanisms of visually induced oscillations and the potential SL motif. The model was trained using backpropagation through time, with rigorous biological constraints, to match spiking statistics (but not oscillation patterns) from the Allen Brain Observatory *in vivo* electrophysiology recordings with Neuropixels probes. We then carried out simulations in which the trained V1 models were visually stimulated with drifting gratings (0.04 cycles/deg, 0.8 contrast, 2 Hz; 8 directions, 10 trials) and naturalistic stimuli (natural scenes, natural movies). Systematic network perturbations were carried out: silencing of interneuron subclasses (Pvalb, Sst, Vip: whole-population and layer-specific groups), layer isolation, and targeted replacement of L4 versus L6 circuit properties. The model reproduced the experimentally observed SL motif, which was preserved across drifting gratings, natural scenes, and natural movies. High-gamma in L4-L5 was contrast- and temporal-frequency-dependent. Among interneuron subclasses, Pvalb silencing produced the largest frequency reorganization; Sst silencing increased alpha/beta power across layers; Vip silencing reduced oscillation magnitude without affecting frequency. Layer-isolation simulations indicated that L4 intrinsically generates high-gamma oscillations that propagate to other layers via interlayer connections. Replacing L4 inhibitory-to-excitatory synaptic parameters with those of L6 suppressed high-gamma and promoted alpha/beta oscillations. Pvalb-to-excitatory synaptic time constants and amplitudes were critical determinants in this effect. Reciprocally, replacing L6 synaptic dynamics with those from L4 shifted L6 from narrow ~20 Hz beta to broadband 20-60 Hz activity. These results suggest Pvalb-to-excitatory synaptic kinetics in L4 as the key circuit mechanism for high-gamma oscillations, with inter-layer connections propagating gamma oscillations across the cortical column, thus offering a potential mechanistic framework for the SL motif.

Disclosures: B. Herrera: None. **S. Ito:** None. **D. Haufler:** None. **K. Dai:** None. **A. Arkhipov:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.02/BB20

Topic: E.06. Vision

Support: NIH Grant R01AG078616
NSF GRFP DGE 2139754

Title: Integrative computations on neuromodulation across macaque cortex

Authors: *A. M. BRIGANDE, A. A. DISNEY;
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Abstract: Dozens of neuromodulators, from small molecules to neuropeptides, vary in concentration across space and time to dynamically influence cortical processing and behavior. How does the cortex solve the high-dimensional problem of integrating neuromodulation? Neuromodulatory systems are often studied individually or pairwise, yet anatomical and functional evidence demonstrates that these systems interact: for example, single neurons respond to multiple neuromodulators. Further complicating matters, many neuromodulators bind multiple receptors with opposing effects on neuronal excitability or synaptic strength, enabling divergent effects from the same neuromodulatory system and convergent effects from different systems. We start from the assertion that the concept of 'integrative computation' applies when considering the ways that neuromodulatory signals interact with and within neurons. By integrative computation, we mean processes in which information across multiple carriers is brought together mathematically - compared or combined, for example - to yield a computed quantity. To get traction on identifying integrative computations on neuromodulation, we measured the signal (neuromodulators) and the filter that reads the signal (receptors) using spatial multi-omics of voxelated cortical hemispheres from two adult female rhesus macaques. For each animal, we approximately flattened and hand-dissected an entire cortical hemisphere at millimeter resolution (either 2.5 or 4 mm), then homogenized and split each sample (233 - 508 samples per animal) to perform targeted metabolomics, a neurotransmitter assay, and deep untargeted proteomics and peptidomics. In the neuromodulator space, we identified and quantified 55 neuropeptides as well as the small molecules acetylcholine, dopamine, histamine, serotonin, and norepinephrine and their metabolites. In the receptor space, we identified and quantified 90 receptors for both small molecules and neuropeptides. We found gradients of neuromodulators and receptors across cortex that provide insight into the spatial organization of neuromodulatory inputs and their integration. To gain cellular resolution in a specific region (primary visual cortex), we performed spatial transcriptomics with coverage of 53 neuropeptides and 162 receptors for another two adult macaques (one female). We found patterns of combinatorial receptor expression by single neurons. Taken together, these data provide a rich spatial map of neuromodulation in primate cortex.

Disclosures: A.M. Brigande: None. **A.A. Disney:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.03/BB21

Topic: E.06. Vision

Support: NIH Grant HD055453
NIH Grant HD108370
NIH Grant NS117597
UCLA Marion Bowen Neurobiology Postdoctoral Scholar Grant Program

Title: Deficits in contextual modulation and receptive field size in the primary visual cortex of Fragile X mice.

Authors: *I. A. TELLO-GARCIA[1], K. POVINEC[1], C. PORTERA-CAILLIAU[1,2];
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Abstract: Atypical sensory processing is a hallmark of Fragile X syndrome (FXS). Previous studies have focused on sensory hypersensitivity and how it contributes to gaze aversion, anxiety, attention deficit, and learning delay. In contrast, differences in sensory integration, which are also prominent in FXS/autism, are less well understood. We investigated differences in circuit function as it relates to visual integration in the primary visual cortex (V1) of *Fmr1* knockout (KO) mice, a well-established model of FXS, relative to their wild type (WT) controls. We used *in vivo* two-photon calcium imaging in *Slc17a7*-Cre, *Pvalb*-Cre, and *Sst*-Flp mice to record, respectively, from excitatory pyramidal (Pyr) neurons, or parvalbumin (PV) and somatostatin (SST) interneurons (IN) in layer 2/3 of V1. We then evaluated receptive field (RF) size, size tuning, orientation selectivity (OS), and surround suppression (SS) for each cell type. Pyr neurons in *Fmr1* KO mice showed enlarged receptive fields ($22.5^{o} \pm 0.4$ vs. $29.4^{o} \pm 0.4$) and were preferentially recruited by larger stimulus sizes compared to WT controls. These differences were associated with significantly enhanced SS, contextual modulation in *Fmr1* KO mice. Parvalbumin (PV) INs from *Fmr1* KO mice exhibited marked hypoactivity, as previously reported, but no differences in size tuning, size preference, or SS. Interestingly, SST INs in *Fmr1* KO mice showed a left-shifted size tuning curve, preferring smaller stimuli and their SS responses were opposite to the canonical pattern observed in WT mice, with a marked increase in their response to a central stimulus (not suppression). Using optogenetics to suppress the firing of SST INs in *Fmr1* KO mice, we are testing whether they contribute to deficits in contextual modulation observed in Pyr neurons. Collectively, these findings will guide an integrative circuit-level evaluation of the role of local inhibitory circuits in visual integration deficits in *Fmr1* KO mice.

Disclosures: I.A. Tello-Garcia: None. **K. Povinec:** None. **C. Portera-Cailliau:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.04/BB22

Topic: E.06. Vision

Support: SC3NS127766
EY17945
P30 EY013079
R21 NS088906
PSC-CUNY 52, 53, 55

PID2024-158727NB-I00
MICIU /AEI /10.13039/501100011033 / FEDER, UE

Title: Ultrastructural Organization of Excitatory Synaptic Boutons in Layers 4B and 6 of Macaque Primary Visual Cortex

Authors: *V. GARCIA-MARIN[1], D. RAMDHANIE[1], L. BLAZQUEZ-LLORCA[2], J. DEFELIPE[3], M. J. HAWKEN[4];
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Abstract: Ultrastructural Organization of Excitatory Synaptic Boutons in Layers 4B and 6 of Macaque Primary Visual Cortex The primary visual cortex (V1) circuitry is made up of different layers that play different roles in processing visual information. In V1 the major thalamic axonal input terminates in layer 4C. Layer 4B receives a dominant feedforward intracortical input from layer 4Cα while layer 6 receives both thalamic and intracortical inputs. Our recent studies have characterized the ultrastructural characteristics of synapses in layer 4C and compared them to layer 3[1]. Here we report on the continued analysis of the detailed ultrastructural properties of excitatory synaptic boutons in layers 4B and 6. Cortical tissue from adult macaque was processed for focused-ion-beam scanning-electron-microscopy (FIBSEM). More than 300 boutons were reconstructed in three dimensions and classified as single-synapse boutons without mitochondria (SSB), single-synapse boutons containing mitochondria (SSBm), or multisynaptic boutons containing mitochondria (MSBm). Bouton volume, synaptic apposition surface (SAS), mitochondrial volume, postsynaptic targets, and synaptic morphology were quantified. In both layers, most boutons formed a single synapse (SSB boutons). While MSBm boutons were less common they were significantly larger, contained greater mitochondrial volume, and formed larger synapses (SAS) than SSB and SSBm boutons, suggesting they may be stronger and more metabolically active connections. Overall bouton volume and synaptic morphology were similar between layers. The main difference was in their postsynaptic targets: boutons in layer 4B more often contacted dendritic shafts, whereas boutons in layer 6 more frequently contacted dendritic spines. Boutons in layer 4B and layer 6 are approximately 1.7 x and 5.2 x times smaller than boutons in layer 3 and 4C, respectively, with MSBm having the largest difference between layers. Together, these results provide new insights into the structural organization of cortical microcircuits and the synaptic basis of information processing in primate visual cortex.
[1]Garcia-Marin V, Hawken MJ. 3D ultrastructural comparison of synapses in thalamic and non-thalamic recipient layers of macaque V1. Cereb Cortex. 2026 Apr 7;36(4):bhag038.

Disclosures: V. Garcia-Marin: None. **D. Ramdhanie:** None. **L. Blazquez-llorca:** None. **J. DeFelipe:** None. **M.J. Hawken:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.05/BB23

Topic: E.06. Vision

Support: NIH Grant U24NS120053

Title: Insights from a visual cortical column connectome

Authors: *B. P. DANSKIN[1], C. ZHANG[1], R. SWANSTROM[1], E. NEACE[1], C. DAVID[2], F. C. COLLMAN[1], N. M. DA COSTA[1], C. M. SCHNEIDER-MIZELL[1];
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Abstract: Publicly-released connectomes provide an incredible testbed for scientific inquiry. Curating these datasets with proofreading and expert annotation is a profound effort, but when complete produces a dense wiring diagram at a scale previously unseen in mammalian cortex. We present here the substantially completed proofreading of a cortical column, a subset of the MICrONS dataset representing a computational and functional unit.
The MICrONS project produced a massively dense reconstruction of the anatomical and functional connections of a millimeter volume of mouse visual cortex. The Virtual Observatory of the Cortex (VORTEX) is our ongoing program to support further refinement and annotation of the dataset, directed by the needs of the scientific community.
We have proofread the axon of every neuron in the 100 μm-spanning 'V1 column' (1355 neurons, 148,000 synapses between known neurons yielding 80,000 unique connections), a subset of the dataset representing a complete functional unit. This sample contains, to our knowledge,every major excitatory cell type in visual cortex, and forms a valuable reference on connectivity of local cortical connections.
Moreover, the cortical column is embedded in the wider network, which is uniquely accessible in the MICrONS dataset. Ongoing proofreading efforts, directed by interest from the scientific community, reveal the neurons within this column make over 1 million synapses to other neurons (766,000 unique connections) within the cubic millimeter sample of visual cortex. We have further increased the diversity of proofread inhibitory neurons in the vicinity of the column, adding 214 cells in a further 75 μm ring around the column--effectively doubling the number of local inhibitory cells available for analysis of the column.
Beyond the neuronal connectome, we have proofread all 120 astrocytes and 60 microglia in the same cortical column, providing the most detailed reconstruction of neuron-glia-vasculature interaction to date. Most recently, we have added organelle segmentation which adds unique insights for cell typing, synaptic strength, and plasticity.
Opportunities remain to explore neuronal circuits, cell type diversity, glial interactions, neurovascular dynamics, subcellular networks, and more. With VORTEX, you can guide where we spend our resources. We are committed to contributing to the advancement of science, and are actively reviewing and accepting requests. Access the data portal and submit a research request at: microns-explorer.org/vortex

Disclosures: B.P. Danskin: None. **C. Zhang:** None. **R. Swanstrom:** None. **E. Neace:** None. **C. David:** None. **F.C. Collman:** None. **N.M. da Costa:** None. **C.M. Schneider-Mizell:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.06/BB24

Topic: E.06. Vision

Title: Ultrastructure-enriched morphology reveals shared and distinct neuronal properties across two millimeter-scale connectomic volumes of mouse visual cortex

Authors: *C. M. SCHNEIDER-MIZELL[1], A. L. BODOR[2], D. BRITTAIN[4], J. BUCHANAN[5], D. J. BUMBARGER[3], E. JOYCE[7], G. MAHALINGAM[6], R. TORRES[8], W. YIN, Esq.[2], M. M. TAKENO[9], R. REID[5], F. C. COLLMAN[8], N. M. DA COSTA[2];
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Abstract: The mammalian cortex is broadly considered to have a canonical circuit organization, repeating within and across cortical regions with minor variations. Millimeter-scale electron microscopy (EM) volumes such as the MICrONS dataset (MICrONS Consortium, 2025) have enabled the characterization of the morphology and synaptic connectivity of thousands of single neurons across layers, linking the cortical circuit to detailed single-cell properties. However, little is known about how the property distributions of entire neuronal populations differ in a coordinated manner between individual animals within the same brain region.
Here, we present "V1dd," a new densely reconstructed millimeter-scale EM volume of mouse primary visual cortex spanning all layers, acquired in a similar manner to the MICrONS volume. To characterize neuronal diversity and cell types within and between volumes, we developed a morphological feature pipeline applied to neuronal dendrites, incorporating perisomatic features (Elabbady et al., 2025), dendritic arbor features (Schneider-Mizell et al., 2025), and dendritic compartments (Pedigo et al., 2026) across more than 62,000 neurons in V1dd and 69,000 in MICrONS.
The resulting feature landscape readily distinguished excitatory and inhibitory neurons in both datasets. Among excitatory neurons, major laminar and projection classes were clear and reproducible, but a more detailed examination revealed some striking differences. For example, layer 4 pyramidal cells showed consistently lower spine density in MICrONS than in V1dd, while layer 6 pyramidal cells showed higher spine density. In addition, a sparsely innervated layer 2 subpopulation present in MICrONS was not found in V1dd. In contrast, for inhibitory neurons, we found no major population-level or laminar differences in feature distributions between datasets, suggesting that inhibitory cells might be more anatomically consistent across individuals than their excitatory neighbors. Understanding this variability and its connectivity consequences has important implications for the coordinated plasticity and development of neuronal populations as well as for calibrating cortical connectomics datasets.

Disclosures: C.M. Schneider-Mizell: None. **A.L. Bodor:** None. **D. Brittain:** None. **J. Buchanan:** None. **D.J. Bumbarger:** None. **E. Joyce:** None. **G. Mahalingam:** None. **R. Torres:** None. **W. Yin:** None. **M.M. Takeno:** None. **R. Reid:** None. **F.C. Collman:** None. **N.M. da Costa:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.07/BB25

Topic: E.06. Vision

Support: NIH U24NS120053

Title: Synaptic architecture of pathway-specific thalamic inputs in mouse visual cortex

Authors: B. P. DANSKIN, ***R. SWANSTROM**, E. NEACE, C. M. SCHNEIDER-MIZELL, N. M. DA COSTA, C. ZHANG;
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Abstract: Thalamocortical (TC) pathways convey diverse streams of information to cortex, from primary sensory signals to higher-order contextual inputs. Yet how these pathways differentially engage cortical circuits remains incompletely understood, especially at the level of single synaptic connections. Here, we leverage the MICrONS large-scale electron microscopy dataset to identify and reconstruct TC axons in mouse primary visual cortex (VISp) and higher visual areas (HVAs) to investigate how synaptic features relate to visual-area- and cell-type-specific connectivity. Across the reconstructed TC axons, we observed distinct axonal morphology and cortical laminar targeting patterns, consistent with axons originating from the core and shell regions of dorsal lateral geniculate nucleus (dLGN) and lateral posterior nucleus (LP) of the thalamus. Putative dLGN-core axons formed dense bushy arbors centered in layer (L) 4. In contrast, putative dLGN-shell axons arborize densely in L2/3. LP axons are generally sparse, with a higher branch density in layer L5 and sparse projections to layer L1. To determine whether these different thalamic pathways employ specialized synaptic strategies, we analyzed individual reconstructed axons at ultrastructural resolution, quantifying synapse morphology, size, divergence, target preference, and spatial organization across postsynaptic cell types. We further examined how different TC pathways engage inhibitory neurons to shape excitatory targets through local disynaptic circuit motifs. Although different TC axons shared synaptic morphological features that distinguished them from corticocortical axons, they exhibited distinct patterns of synaptic connectivity across cortical cell types. Furthermore, individual LGN axons with arborizations spanning multiple visual cortical areas displayed three area-specific targeting profiles:. two primary arbors, with a larger, more complex arbor in VISp and a smaller arbor in an HVA, accompanied by preferential targeting of superficial and deep layers, respectively; a dominant VISp arbor with one or two branches extending into an HVA, typically through layer 4; and a single primary arbor spanning the VISp-HVA boundary. Together, these findings extend beyond projection anatomy to uncover pathway-specific synaptic architectures of thalamic input, revealing how distinct thalamic pathways may differentially participate in cortical computation through specialized patterns of synaptic organization.

Disclosures: B.P. Danskin: None. **R. Swanstrom:** None. **E. Neace:** None. **C.M. Schneider-Mizell:** None. **N.M. da Costa:** None. **C. Zhang:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.08/BB26

Topic: E.06. Vision

Support: Paul G Allen grant

Title: Hypertargeting: connections of extraordinary strength onto interneurons of unusual character in the mouse visual cortex

Authors: *C. ZHANG, A. L. BODOR, B. D. PEDIGO, L. ELABBADY, S. RATH, C. M. SCHNEIDER-MIZELL, F. C. COLLMAN, N. M. DA COSTA;
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Abstract: Projections from the raphe nuclei broadly innervate the neocortex and are thought to regulate cortical state, sensory processing, and plasticity. However, the synaptic organization through which axons engage local cortical circuits remains poorly understood. To identify the circuit motifs underlying modulation originating from raphe, we leveraged the MICrONS electron microscopy dataset of mouse visual cortex to reconstruct long-range axons and their postsynaptic targets at synaptic resolution. We identified a population of long-range axons exhibiting an unusual hypertargeting pattern, in which individual axons often formed more than 25 synapses onto single inhibitory neurons and up to 175 synapses, but fewer than 5 synapses onto individual excitatory neurons. These axons were primarily located in layers 1-2 and occasionally extended branches into deeper layers. The targeted interneurons displayed highly stereotyped axonal morphology, including flattened disc-like output varicosities and distinctive bowtie-like axonal segments containing a large pool of vesicles with variable morphology but lacking synaptic contacts. Across reconstructed cells, these interneurons preferentially innervate layer 2 intratelencephalic (IT) neurons. Based on the laminar distribution, morphology, and synaptic organization, we propose that the hypertargeting axons are vGluT3-positive projections from the raphe nuclei and that their postsynaptic targets are CCK-positive interneurons. Complementary immunohistochemical analyses in mouse cortex further support these proposed cellular identities. The presence of serotonin in the hypertargeting axons requires further confirmation.Our results reveal a previously undescribed circuit motif in the cortex, characterized by extreme synaptic convergence onto a morphologically and connectivity-defined interneuron population, suggesting the existence of a privileged inhibitory pathway for regulation of cortical circuits from raphe-driven through CCK-positive basket cells.

Disclosures: C. Zhang: None. **A.L. Bodor:** None. **B.D. Pedigo:** None. **L. Elabbady:** None. **S. Rath:** None. **C.M. Schneider-Mizell:** None. **F.C. Collman:** None. **N.M. da Costa:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.09/BB27

Topic: E.06. Vision

Support: ANR-25-CE16-3517

Title: A non-canonical SST interneuron-pyramidal neuron signaling axis gates cortical NMDAR function

Authors: *D. DHANASOBHON[1], A. I. ARAYA MARTÍNEZ[1], E. BERTHAUX[1], C. MARTINS PINHO[1], Y. ZERLAUT[1], C. CHARRIER[2], L. TRICOIRE[3], N. A. REBOLA[1]; [1]Paris Brain Inst. (ICM), Paris, France; [2]Inserm, Paris, ; [3]Neurosci. Paris Seine UMR8246, Ctr. Natl. de la Recherche Scientifique, Paris, France

Abstract: Interneurons are best known for controlling cortical pyramidal neuron activity through GABAergic inhibition, thereby shaping pyramidal cell firing and synaptic plasticity. Here, we identify an unexpected non-canonical signaling axis, independent of GABAergic synaptic signaling, that links GluN1/GluN3A excitatory glycine receptors (eGlyRs) in somatostatin interneurons (SST-INs) to glutamate delta receptor 1 (GluD1)-dependent regulation of synaptic N-methyl-D-aspartate receptor (NMDAR) function in layer 2/3 pyramidal neurons of adult mouse primary visual cortex. This pathway connects two atypical members of the ionotropic glutamate receptor family: eGlyRs, which are enriched in SST-INs, and GluDs, which regulate synaptic signaling beyond their roles as synaptic organizers. Using whole-cell recordings in acute cortical slices, cell-type-specific genetic manipulations, and pharmacology, we found that function of synaptic NMDAR in pyramidal neuron depends on SST-IN eGlyRs and GluD signaling. Application of EU1180-438, a GluN3A negative allosteric modulator, enhanced synaptic NMDAR currents in L2/3 pyramidal neurons. This effect was abolished after SST-IN-specific GluN3A knockdown, identifying SST-IN eGlyRs as necessary components of this trans-cellular pathway. Similarly, EU1180-438 failed to enhance NMDAR currents in serine racemase knockout mice and under GluD1-deficient conditions, suggesting that endogenous D-serine and GluD1 are both required for eGlyR-dependent modulation. We next investigated cerebellin-4 (Cbln4), a GluD-associated ligand linked to SST-IN signaling. Selective removal of Cbln4 from SST-INs abolished the NMDAR potentiation induced by eGlyR inhibition, demonstrating that SST-derived Cbln4 is required for this effect. These findings suggest that SST-IN eGlyRs engage a Cbln4-GluD1 signaling mechanism to regulate postsynaptic NMDAR gain in neighboring pyramidal neurons. We are now testing how this axis regulates synaptic plasticity in L2/3 pyramidal neurons in adult V1. Preliminary data suggest that this novel pathway controls LTP induction in these cells, revealing that interneurons can regulate plasticity in neighboring pyramidal neurons independently of GABAergic synaptic signaling. In parallel, ongoing in vivo two-photon calcium imaging in V1 pyramidal neurons is being used to determine how this signaling mechanism contributes to the encoding and stability of visual representations in adult

V1. Overall, these findings identify an SST-IN eGlyR-Cbln4-GluD1 pathway that gates pyramidal neuron NMDAR function, linking interneuron signaling to cortical plasticity and sensory computation.

Disclosures: D. Dhanasobhon: None. **A.I. Araya Martínez:** None. **E. Berthaux:** None. **C. Martins Pinho:** None. **Y. zerlaut:** None. **C. Charrier:** None. **L. Tricoire:** None. **N.A. Rebola:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.10/BB28

Topic: E.06. Vision

Support: NIH R34NS128890
NIH UO1 NS120822

Title: Voltage dynamics of cortical layer 1 interneurons in sensorimotor integration

Authors: *K. S. MCCLUSKEY[1], S. ABBASPOUR[2], A. KANG[2], S. RAFIEI[2], G. VASAN[2], M. KANNAN[2];
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Abstract: To successfully navigate their environment, animals must distinguish between self-generated sensory stimuli, arising from their own locomotor activity, and externally generated stimuli from their environment, and respond promptly and appropriately when the two diverge. The neural and cellular mechanisms by which motor and sensory information are integrated in sensory cortical areas to enable this distinction, and therefore allow for behavioral adaptation, are unknown. Work in primary visual cortex (V1), using the visuomotor mismatch paradigm, has shown that layer 2/3 pyramidal neurons respond to discrepancies between motor predictions and actual sensory feedback by exhibiting signed mismatch responses across distinct subsets of neurons (Jordan and Keller, 2020). However, the cell-class-specific logic that underlies this computation remains unaddressed. Here, we show that the V1 layer 1 GABAergic interneurons are a candidate cortical substrate in this computation. Using anatomical tracing and *ex vivo* electrophysiology, we determine that V1 L1 interneurons receive descending input from a distal motor area and a higher-order thalamic nucleus, both implicated in conveying motor predictions and prediction error signals to V1. L1 interneurons are also innervated by recurrent inputs from within V1, carrying ascending sensory signals. In high-speed (640 Hz) pAce voltage imaging (Kannan et al., 2022) in head-fixed, running mice, we find that V1 L1 interneurons exhibit motor-anticipatory activity in complete darkness but also show stimulus selectivity during visual presentations, further corroborating their role as integrators of motor and sensory signals. In mice navigating a virtual visual corridor, where their running speed controls the speed of oncoming visual flow, V1 L1 interneurons respond to brief visuomotor mismatches, when the two speeds

are decoupled. Crucially, their responses are bidirectional: some mismatch-modulated neurons increase while others decrease their firing rates at mismatch onset. Our observations suggest a functional heterogeneity within this population, creating the need for a more granular assessment of molecular or input-defined approaches to determine its anatomical basis. Overall, our work directly aligns with the predictive coding framework and suggests that L1 neurons may be uniquely poised to integrate motor and sensory streams in sensory-guided navigation and that a disruption of their activity may not only interfere with the generation of the signed mismatch responses in cortical microcircuits but also impair error-driven behavioral correction.

Disclosures: K.S. McCluskey: None. **S. Abbaspour:** None. **A. Kang:** None. **S. Rafiei:** None. **G. Vasan:** None. **M. Kannan:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.11/BB29

Topic: E.06. Vision

Support: NIH Grant R34NS128890
NIH Grant U01 NS120822

Title: Molecular subclass-specific interrogation of cortical interneuron voltage dynamics

Authors: *S. ABBASPOUR[1], S. MORRIS[1], G. VASAN[2], M. KANNAN[2];
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Abstract: The mammalian neocortex achieves a remarkable division of labor in awake behavior, enabling the seamless integration of ascending sensory signals from peripheral areas with descending contextual, attentional, and predictive information from top-down streams. A substrate for this functional specialization is thought to lie in the vast molecular diversity of cortical neurons. While this correspondence is well-established for excitatory neurons, it is less explored among interneurons. Nonetheless, molecular subclasses nested within major interneuron classes exhibit distinct laminar distributions, afferent and efferent connectivity patterns, and even subcellular preferences in their synaptic targets (Wu et al., 2023; Patiño et al., 2024). Differences in state-modulated interneuronal dynamics can also be inferred from their relative position along the transcriptomic axis (Bugeon et al., 2022). Yet much of this evidence is indirect, *post-hoc* validated, or agnostic to spike-resolved dynamics, within which fine temporal distinctions in activation patterns among subclasses remain buried. A fundamental understanding of whether molecular subclasses represent non-redundant functional cell types requires an approach that (1) accesses their real-time spike-timing dynamics *in vivo*, and (2) allows spike recordings to be performed simultaneously from multiple subclasses to resolve fine temporal differences that are invisible to single-population averaging. Here, we developed Boolean intersectional targeting of our FRET-opsin genetically encoded fluorescent voltage indicators

(GEVIs)—Ace-mNeon2 and pAce (Kannan et al., 2022)—enabling their selective expression in interneuron subclasses nested within broader genetic types. Because Ace-mNeon2 and pAce exhibit opposite fluorescence response polarities but operate in the same spectral channel, the identity of each recorded neuron is inferred unambiguously from the directionality of their optical spike waveform, without multi-color optics. Using this approach in primary visual cortex of behaving mice, we obtain simultaneous, single-neuron, single-spike-resolution recordings from multiple molecular subclasses, capturing correlated spiking, trial-to-trial co-variability arising from shared inputs, and response latency differences in the same trials. We resolve the functional role of molecular types across multiple functional domains: visual tuning properties, motor responses, state modulation, and predictive signaling. Our findings reveal how the molecular diversity of cortical interneurons underwrites a functional division of labor in behaving animals.

Disclosures: S. Abbaspour: None. **S. Morris:** None. **G. Vasan:** None. **M. Kannan:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.12/BB30

Topic: E.06. Vision

Support: NIH Grant U01MH130907

Title: Diversity of visual responses across transcriptomic cell types in the mouse primary visual cortex

Authors: *O. ZOBEIRI[1], H. SCHRYVER[2], J. KIM[1], J. CAMPOS[1], N. MARTIN[5], P. OLSEN[5], S. M. SEID[7], A. OYAMA[6], C. KIM[5], S. D. HASTINGS[5], S. MCCULLOCH[1], A. WILLIFORD[1], A. LEON[9], D. MCMILLEN[3], M. S. ALOI[4], S. R. OLSEN[1], P. A. GROBLEWSKI[8], J. WATERS[8], M. E. GARRETT[10], A. ARKHIPOV[1];
[2]Modeling & Theory, [3]Imaging, [4]Psychiatry, [1]Allen Inst., Seattle, WA; [6]Mol. Biol. - Histology, [5]Allen Inst. for Brain Sci., Seattle, WA; [7]Allen Inst. For Brain Sci., Kent, WA; [8]Allen Inst. For Brain Sci., Seattle, WA; [9]Neural Dynamics, The Allen Inst., Seattle, WA; [10]Neural Circuits and Behavior, Allen Inst. for Neural Dynamics, Seattle, WA

Abstract: Understanding how genetically defined cell types encode sensory information requires linking in-vivo neural activity to transcriptomic identity at single-cell resolution. Here we present a framework for linking functional characterization of pan-neuronal populations with their gene expression profiles across the full Allen Institute transcriptomic hierarchy, from subclass to supertype to cluster, in the mouse primary visual cortex (V1).We performed large-scale multiplane two-photon calcium imaging in pan-neuronal cell populations in mouse V1, recording across multiple cortical layers (~1000-1,200 neurons/mouse) during passive presentation of drifting gratings (3 sessions) and natural movies (1 session). Post-hoc spatial transcriptomics was

performed using the Xenium in-situ platform on serial 20-µm sections of the imaged cortical volume. To link the two modalities, we developed a semi-automated co-registration pipeline: (1) targeted sectioning is guided by surface vasculature to localize the imaged field; (2) Xenium sections are then automatically elastically warped to match the in vivo 2p z-stack; and (3) cell masks are automatically matched across modalities. This pipeline yielded ~800-1000 co-registered neurons for each mouse, with each neuron then classified into excitatory (mostly L2/3 IT, L4/5 IT) and inhibitory (Pvalb, Sst, Vip, Lamp5) subclasses, supertypes, and clusters using the Allen Institute hierarchical taxonomy.Functional responses at the subclass level were consistent with earlier Cre-line data, validating the pan-neuronal approach: Vip neurons preferred lower contrasts, Sst neurons preferred higher contrasts, and L2/3 and L4/5 IT neurons preferred lower temporal frequencies. Multi-session recordings revealed that Vip responses varied substantially across days, while Sst responses remained stable. At the supertype level within L4/5 IT, we identified functionally divergent populations: while one supertype increased its activity with temporal frequency, the activity of another supertype decreased. At the cluster level, Pvalb neurons partitioned into low- and high-contrast-preferring subpopulations that corresponded to specific transcriptomic Pvalb clusters. These results establish a scalable pan-neuronal pipeline for linking transcriptomic identity to in vivo visual function, revealing a structured correspondence between gene expression and neural coding that extends to the finest levels of the transcriptomic hierarchy.

Disclosures: O. Zobeiri: None. **H. Schryver:** None. **J. Kim:** None. **J. Campos:** None. **N. Martin:** None. **P. Olsen:** None. **S.M. Seid:** None. **A. Oyama:** None. **C. Kim:** None. **S.D. Hastings:** None. **S. McCulloch:** None. **A. Williford:** None. **A. Leon:** None. **D. McMillen:** None. **M.S. Aloi:** None. **S.R. Olsen:** None. **P.A. Groblewski:** None. **J. Waters:** None. **M.E. Garrett:** None. **A. Arkhipov:** None.

Poster

PSTR230: Visual Cortex: Cell Types and Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR230.13/BB31

Topic: J.03. Anatomical Methods

Support: NIH R24MH114785
NIH 1U01NS137250

Title: Surround Suppression Across Cortical Depth in Mouse Visual Cortex: Functional Connectomics Identifies MET-8 Martinotti Cells as a Candidate Cellular Substrate

Authors: *P. K. RIVLIN[1], M. HU[2], J. MATELSKY[1], J. REIMER[2], B. A. WESTER[1]; [1]Johns Hopkins Applied Physics Lab., Laurel, MD; [2]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Although somatostatin-containing (SST) interneurons have been implicated in surround suppression across visual cortical layers, the SST subtypes supporting this computation remain unknown. Hendricks et al. (2026) recently proposed a “like-to-like” connectivity motif in layer 2/3 in which SST neurons integrate co-tuned center- and surround-responsive pyramidal cell (PC) input and participate in recurrent inhibitory loops with similarly tuned local PCs. Whether analogous circuit motifs exist in deeper cortical layers is unknown. To address this, we leveraged the MICrONS functional connectomic dataset, a cubic millimeter of mouse visual cortex combining electron microscopic reconstruction with *in vivo* calcium imaging during visual stimulation (MICrONS et al. 2025). Building on morpho-electric-transcriptomic (MET) classification of layer 4/5 Martinotti cells (MCs) in the MICrONS volume (Gamlin et al. 2025) and ongoing proofreading to correct errors in neuronal reconstructions (microns-explorer.org), we identified additional candidate MET-8 cells among 113 proofread, unclassified MCs through unsupervised clustering and subsequent morphological and connectivity validation. Our interest in the MET-8 subtype arose from analysis of an initially unclassified MC (MC-7787) that, based on comparison with curated MET types, was classified as MET-8, and exhibited a connectivity motif reminiscent of the surround-suppression circuit proposed for layer 2/3 SST cells. Specifically, MC-7787 received convergent input from both local and distant layer 2/3 and layer 4 PCs, suggesting integration of information across spatially distributed visual representations. This observation motivated a systematic analysis of the functional properties of PCs presynaptic to MET-8 using functional “digital twin” data (Wang et al. 2025; Ding et al. 2025). Across the population of functionally co-registered PC partners of MET-8 cells, we found evidence for a like-to-like connectivity organization. Reciprocal PC-MC pairs were significantly more iso-oriented than unidirectional PC→MC pairs at PC-MC intersomatic distances < 200 μm. Moreover, per-cell regression analyses revealed a robust output-arm tuning relationship between MET-8 cells and their postsynaptic PC targets. Together, these findings identify MET-8 MCs as a candidate cellular substrate for surround suppression and suggest that like-to-like SST motifs may represent a conserved circuit principle across cortical depth.

Disclosures: P.K. Rivlin: None. **M. Hu:** None. **J. Matelsky:** None. **J. Reimer:** None. **B.A. Wester:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.01/Web Only

Topic: E.06. Vision

Support: Brain Science and Brain-like Intelligence Technology—National Science and Technology Major Project (2022ZD0208200)

Title: Population Representation of Global Visual Symmetry in Macaque TEO

Authors: *S. LI, W. LI, Y. YAN;
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Abstract: Objective Visual symmetry is fundamental to perceptual organization, yet its neuralrepresentation in the primate brain remains poorly understood. We investigated bilateralsymmetry encoding in the posterior inferotemporal cortex (area TEO), a key stage of the ventralvisual stream. **Methods** We recorded multi-unit activity (MUA) via 64-channel microelectrodearrays in area TEO of two rhesus macaques during a passive fixation task. Stimuli werespecifically designed to dissociate global symmetry from local feature-based cues, ensuring neuralresponses reflected symmetry processing rather than low-level shape confounds. **Results** (1)Fisher Linear Discriminant (FLD) analysis revealed that TEO neuronal populations effectivelydifferentiated symmetric from asymmetric patterns. This discriminative performance wassignificantly higher than the classification accuracy for shapes, providing evidence for specializedsymmetry-based encoding. (2) Analysis of the neural encoding space further demonstrated thatsymmetry is not a mere modulation of shape-related tuning but emerges as a standalone featurethat operates independently of shape representation. (3) These encoding patterns were anchored tothe axis of symmetry; population representation remained invariant across different shapes whenthe axis was fixed, but shifted significantly when the axis was modified. **Conclusion** Area TEOcontains robust population signals selective for bilateral symmetry. This encoding transcendsarbitrary stimulus partitions and is organized around the symmetry axis, highlighting TEO as akey cortical site for extracting global structural regularities.

Disclosures: S. Li: None. **W. Li:** None. **Y. Yan:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.02/BB32

Topic: E.06. Vision

Support: NIH 5R01NS127107
Simons 542999
Simons 2794-08

Title: Linking inter-areal signaling and visual computation in macaque V1 and MT

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Abstract: Brain function emerges from structured communication between neuronal populations. Advances in large-scale neural recordings and analytic methods now make it possible to identify the flow of population activity across areas, yet how such inter-areal signaling contributes to specific cortical computations is poorly understood. To investigate the

relationship between signaling and computation, we focused on the macaque motion processing pathway involving primary visual cortex (V1) and area MT. The V1-MT circuit plays an important role in motion processing, and there are strong candidate models for this processing and for the visual response properties of its neurons. These features make this circuit a tractable system for assessing inter-areal signaling in an established computational framework. We simultaneously recorded population activity from V1 and MT using two Neuropixels probes while an awake monkey passively viewed gratings and plaids varying in motion direction, stimulus size, and contrast. To understand signaling between areas, we applied Delayed Latents Across Groups (DLAG), a dimensionality reduction model that identifies shared time-varying latent activity, dissociates within-area and across-area components, and infers delayed interactions between neural populations. In preliminary analyses, DLAG identified both within-area and across-area latents, revealing distinct feedforward and feedback signatures and suggesting selective bidirectional communication between V1 and MT. Ongoing analyses will test how these signals depend on stimulus properties and how each latent signal shapes neuronal response properties, thereby linking population-level signaling to visual computation.

Disclosures: H. Ma: None. **A. Kohn:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.03/CC1

Topic: E.06. Vision

Support: Brain Science and Brain-like Intelligence Technology—National Science and Technology Major Project (2022ZD0208200)
Brain Science and Brain-like Intelligence Technology—National Science and Technology Major Project (2022ZD0204600)

Title: A Specialized Neuronal Subpopulation in Area TEO Links Learning-to-Learn and Generalization

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Abstract: Learning enables animals to adapt to changing environments by improving the neural representation of behaviorally relevant information. However, the utility of learning would be limited if its benefits remained restricted to previously trained stimuli. Two mechanisms help overcome this limitation: accelerated acquisition of new information, known as learning-to-learn, and the generalization of learned representations to novel stimuli. Whether these two processes

rely on a common neural substrate remains unknown.To address this question, we chronically recorded neuronal population activity using multielectrode arrays in cortical area TEO of macaque monkeys performing a contour detection task. Monkeys were first trained to detect collinear contours of one orientation and were subsequently trained on contours of a novel orientation, allowing us to examine behavioral and neural dynamics across sequential learning stages.Behaviorally, monkeys exhibited a typical orientation-specific improvement after the initial training phase and a significantly accelerated learning rate during training on the novel orientation. To identify neural correlates of this accelerated learning, we tracked contour-related neuronal responses across stages and isolated a distinct neuronal subpopulation whose contour-coding sensitivity (d') increased substantially more rapidly during the second learning phase than during the first. At the population level, Fisher linear discriminant analyses revealed that information encoded by this subpopulation partially generalized across orientations. Consistent with this finding, cross-decoding analyses showed that these neurons developed an orientation-invariant representation of contours, a property that was absent in neurons lacking learning-to-learn characteristics. Moreover, during the second learning phase, activity within this specialized subpopulation became more strongly correlated with the monkeys' behavioral choices, suggesting enhanced utilization by downstream decision-making circuits.Together, these findings identify a specialized cortical subpopulation that links accelerated learning with representational generalization. By providing a generalized representation that can be readily transferred to novel stimuli, this neuronal subpopulation may play an instructive role in enabling efficient learning across related tasks.

Disclosures: S. Wang: None. **R. guo:** None. **W. Li:** None. **Y. Yan:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.04/CC2

Topic: E.06. Vision

Support: NIH Grant R00EY031795
NIH Grant R21EY036566
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Linking neural border ownership signals in V4 to perception

Authors: M. AZADI, *T. P. FRANKEN;
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Abstract: To make sense of visual input, the brain must segment scenes into an organized representation of object surfaces. A prominent segmentation signal in primate visual cortex is provided by border ownership neurons. These neurons signal which side of a border in their

classical receptive field (cRF) is foreground. We recently found that macaque cortical Area V4 contains columnar clusters of border ownership neurons. An important open question is the relation between these neurons and perception, because no study has recorded from them during a scene segmentation task. Here we address this gap by using a novel paradigm to compare border ownership signals with the animal's percept on a trial-by-trial basis. We designed a stimulus in which two abutting surfaces compete for ownership of a common border. We manipulated the ambiguity of border ownership by varying relative depth using binocular disparity: the surface that is near relative to the other surface owns the common border. We kept the common border horizontal, such that it did not carry depth information. We trained a male macaque to report the side of foreground by making a saccade to one of two choice targets. To decorrelate the perceptual choice from the saccade vector, we randomly varied the position of the choice targets between trials. During the task we recorded from single and multiunits in V4 using Neuropixels probes, positioning the scenes such that only the common border overlapped with the cRFs. The monkey's choice varied systematically with relative depth, yielding a smooth psychometric function. V4 units were often strongly tuned for the polarity of depth across the common border (thus border ownership). We compared the tuning of individual units with the animal's percept by computing choice probabilities (CP, the probability that the firing rate for a choice in favor of the unit's preferred side of ownership is larger than that for the opposite choice) for a fixed, ambiguous scene. We find a larger number of border ownership units with statistically significant CP than expected by chance, and for most of these, the prediction of choice is consistent with the preferred side of border ownership (CP > 0.5). Finally, we find that random forest classifiers trained on spike counts to unambiguous scenes from all simultaneously recorded units in a penetration can separate trials with opposite choices for ambiguous scenes better than expected by chance (area under the ROC curve > 0.5). Together, our data suggest that border ownership signals in V4 predict perception in a scene segmentation task.

Disclosures: M. Azadi: None. **T.P. Franken:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.05/CC3

Topic: E.06. Vision

Support: Deutsche Forschungsgemeinschaft (DFG), Project ID 122679504 - SFB 874, D.J.
Deutsche Forschungsgemeinschaft (DFG), JA 945/5-1, D.J.
Deutsche Forschungsgemeinschaft (DFG), Project number 492434978 - GRK 2862/1, Subproject 10, D.J.
US National Institutes of Health BRAIN Initiative Grant (5U01NS099573), T.K.
Lee Kuan Yew Postdoctoral Fellowship administered by Nanyang Technological University Singapore (022506-00001), C.S.
Open Fund Young Individual Research Grant (MOH-001720) administered by the Singapore Ministry of Health's National Medical Research Council, C.S.

Title: Cortex-wide psychedelic-induced coherence and anesthesia-induced decoherence of on-going activity in mice

Authors: *C. WHITE[1], C. SONG[2], T. KNOPFEL[3], D. JANCKE[4];
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Abstract: Although the consciousness-altering effects of drugs such as anesthetics and psychedelics are well-established, their effects on cortex-wide activity at high spatiotemporal resolution is less understood.
Utilizing wide-field optical imaging at high spatial and temporal resolutions, we recorded fluorescent signals reflecting membrane potentials across cortical neuronal populations in mice that genetically encode voltage indicators in layer 2/3 and 5 pyramidal neurons. Experiments were conducted under three conditions: resting waking state, anesthetized, and post injection of a hallucinogenic 5-HT2A agonist.
Previously, it has been shown that psychedelics can modulate visual processing into a top-down state, which is often linked to a change in consciousness. As many hypotheses of consciousness rely on brain-wide coherence dynamics, we were particularly interested in the holistic nature of ongoing cortical activity. Here, we analyse the phase of the most dominant frequency for each image pixel - representing average postsynaptic dendritic activity of neuronal populations - and characterise the cortex-wide temporal dynamics of coherence across conditions. During the resting waking state we observe a stable fragmented distribution of phases. In contrast, in both conditions of altered consciousness, we revealed cortex-wide patterns of coherent activity. Psychedelics (DOI and TCB-2) induced oscillations between strong cortex-wide coherence and decoherence. While under anesthesia (isoflurane) we observe decoherence. These findings are consistent with prominent hypotheses, which describe metastability or entropy to play a crucial role in understanding consciousness.
Overall, the observed changes in cortex-wide dynamics during states of altered consciousness point towards neural mechanisms that involve massive changes in brain-wide coherence.

Disclosures: C. White: None. **C. Song:** None. **T. Knopfel:** None. **D. Jancke:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.06/CC4

Topic: E.06. Vision

Support: NSF IIS-2113197
NIH 1R01EY037347-01
NIH 1ZIAEY000558

Title: Deep neural networks with high temporal resolution enhances computational distinctions of V1 neurons

Authors: *I. FERNANDEZ[1], M. GREENE[2], V. KUGATHASAN[1], R. BARTOLO[3], J. ANTOLIK[4], B. R. CONWAY[5], D. A. BUTTS[6];
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Abstract: Inputs to the visual system are spatiotemporal: animated by movement in the world, and especially self-motion and eye movements. Likewise, neurons in the primary visual cortex (V1) can respond precisely in time to natural spatiotemporal stimuli, with latencies corresponding not only to their own selectivity but also to their location in the cortical circuit. However, data-driven deep neural networks (DNNs) of V1 - which can be quite successful at predicting neural responses - generally neglect temporal processing: either explicitly by fitting to neural responses to flashed images, or implicitly by isolating temporal processing to the model's input stage. To use such DNNs to elucidate the function of neurons in V1, we assert that temporal processing at sufficiently high resolution must be treated as a key factor in model architecture. Here, we introduce predictive models of V1 neurons that distribute temporal processing throughout the network, not just at the input stage, with the goal of better elucidating functional distinctions between V1 neurons. We use two types of data: one produced by a large-scale “realistic” dynamical simulation of V1 neurons, where the computation performed by each neuron is known, and another produced from recordings in fixating animals. For both datasets, we use a recently introduced method of “computational barcodes” to distinguish the range of computations present across the V1 population. Each neuron's "barcode" is a vector that encodes the computations produced by the model, necessary to predict the neuron's response, such that neurons with similar barcodes share similar computations. Indeed, we find that using DNNs that explicitly incorporate temporal processing at high resolution results in barcodes that are better able to distinguish computational differences. In fact, models trained at higher temporal resolutions outperform those trained at the base sampling rate. In the simulation data, where the ground truth computational distinctions are known, temporally precise models more accurately capture the known computational distinctions across its simulated neural population. These findings suggest that incorporating distributed temporal processing at higher time resolution into DNN models of sensory systems can improve predictive performance and better align learned computations by the model with the true computations of the cortex.

Disclosures: I. Fernandez: None. **M. Greene:** None. **V. Kugathasan:** None. **R. Bartolo:** None. **J. Antolik:** None. **B.R. Conway:** None. **D.A. Butts:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.07/CC5

Topic: E.06. Vision

Support: ZIAMH002966

Title: Human population orientation maps depend on spatial frequency selectivity

Authors: *A. KUO[1], J. L. GARDNER[2], E. P. MERRIAM[1];
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Abstract: Population neural measurements in both rodents (with Ca2+ imaging) and humans (with BOLD fMRI) have consistently found orientation selectivity associated with the stimulus aperture edge, a phenomenon termed 'stimulus vignetting.' Computational theory suggests that this apparent orientation selectivity can arise from spatial frequency tuning alone, even in populations of neurons (e.g., as measured by fMRI voxels) that completely lack intrinsic orientation selectivity. Computational models of stimulus vignetting make a non-intuitive prediction: orientation preference due to stimulus vignetting should depend on the spatial frequency content of a stimulus, whereas intrinsic orientation preference should be invariant to stimulus spatial frequency. To test this prediction, we measured BOLD fMRI population responses in human visual cortex to oriented gratings (circular annulus: 2.5 deg inner radius, 5 deg outer radius; orientations: 0, 11.25, ⋯, 168.75 deg) across a span of spatial frequencies (0.5-12 cycles/deg). We found that stimuli with low spatial frequencies produced maps of orientation preferences that were radial in structure, with each voxel preferring an orientation pointing inward toward the fovea. This observation is consistent with many prior reports of a radial orientation bias in human fMRI measurements. However, stimuli with high spatial frequency content produced maps of orientation preferences tangential to those from the radial maps, indicating a 90 degree shift in preference, confirming the theoretical prediction. A multivoxel decoder reliably classified stimulus orientation when training and testing on population responses to stimuli of the same spatial frequency. However, cross-decoding performance, i.e., training a decoder on responses to low spatial frequency responses then testing on high spatial frequency responses, and vice versa, was consistently below chance due to systematic decoder errors for the incorrect orthogonal orientation. Cross-decoding performance was rescued by shifting orientation labels by 90 degrees. Our results demonstrate that stimulus vignetting provides the dominant orientation signal measured in fMRI responses to oriented gratings.

Disclosures: A. Kuo: None. **J.L. Gardner:** None. **E.P. Merriam:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.08/CC6

Topic: E.06. Vision

Title: Interrelationship between Orientation and Spatial Frequency Coding in Macaque V1

Authors: X. WANG[1], S. TANG[1], ***C. YU**[2];
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Abstract: Orientation and spatial frequency are two fundamental dimensions of visual coding in primary visual cortex (V1), but how these features are jointly represented and recovered from population activity remains unclear. This question is particularly important for low spatial frequencies, where neurons with strong single-cell selectivity are relatively scarce. We examined the interrelationship between orientation and spatial frequency coding using two-photon calcium imaging to record large-scale population responses from macaque V1 across four fields of view, each containing more than 1000 neurons. Stimuli consisted of 216 Gabor patterns that systematically varied in orientation, spatial frequency, and size. Principal component analysis revealed that responses to different spatial frequencies formed distinct manifolds in population representational space, including low spatial frequencies that were weakly represented at the single-neuron level. Within each frequency-specific manifold, responses to different orientations and sizes showed structured organization, allowing us to estimate orientation discriminability as a function of spatial frequency. Manifold volume increased with spatial frequency, peaked at 4 cpd, and declined at 8 cpd, indicating that orientation information is most strongly separated at intermediate spatial frequencies. We further trained a transformer-based decoder to reconstruct the visual stimuli from V1 population activity. The decoder achieved high reconstruction accuracy, and attention-based ablation revealed frequency-dependent sequences of feature recovery. For mid-to-high spatial frequencies, orientation was recovered before spatial frequency, whereas for low spatial frequencies, spatial frequency emerged first or together with orientation. These results suggest that orientation and spatial frequency are not independently decoded from V1 population activity. Instead, their relationship depends on spatial frequency scale: low spatial frequencies provide coarse global structure, whereas intermediate spatial frequencies support stronger orientation discrimination. Thus, macaque V1 population activity jointly represents orientation and spatial frequency through structured population geometry and supports a coarse-to-fine reconstruction of visual features.

Disclosures: X. wang: None. **S. Tang:** None. **C. Yu:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.09/CC7

Topic: E.06. Vision

Title: Interpretable neural-image alignment suggests a robust structural scaffold in macaque V1 population activity

Authors: *X. WANG[1], S. TANG[2], C. YU[3];
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Abstract: Current encoding and decoding models can predict neural responses to natural images and identify natural images from neural activity, but they provide limited insight into how population activity represents visual scene structure. Here, we propose a Dual Alignment Model, an interpretable contrastive framework that aligns natural images and monkey V1 population responses in a shared latent feature-map space. By representing image and neural signals as comparable spatial feature maps, the framework shifts neural-image correspondence from stimulus identification to representation analysis. It also enables direct visualization and quantitative comparison of the visual structures recoverable from V1 population activity.We recorded large-scale two-photon calcium imaging data from awake, fixating monkey V1 while the monkeys were passively viewing natural image. Model analysis indicated that the aligned feature maps revealed a coarse, low-dimensional structural scaffold of natural images. This scaffold preserved broad spatial organization of natural images while suppressing fine-grained pixel-level details. Therefore, V1-compatible population representations may not simply mirror sharp local image structure but instead emphasize a compact and stable organization of image layout. Perturbation analyses further showed that, compared to fine-grained image features, this scaffold was more stable when influenced by noise, blur, and contrast reduction. This indicates that V1 population activity may prioritize robust structural organization in addition to supporting stimulus discrimination. Interpretability analyses further showed that the scaffold was supported by distributed informative image regions containing shape-like, texture-like, and mixed cues. Moreover, neural-subset analyses revealed that the scaffold could be efficiently recovered from sparse, stimulus-dependent subsets of strongly responsive neurons, suggesting that natural scene structure is accessed through flexible population readout rather than a fixed uniform contribution from all recorded neurons.Together, these findings suggest that monkey V1 population activity supports a robust, stimulus-dependent structural scaffold for natural images by integrating diverse visual cues across distributed neural responses. More broadly, the interpretable contrastive alignment framework provides a principled approach for probing the organizing principles of population-level neural representations.

Disclosures: X. wang: None. **S. Tang:** None. **C. Yu:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.10/CC8

Topic: E.06. Vision

Support: NIH Grant MH130413

Title: NeuralMI: Scalable information-theoretic analysis for high-dimensional neural recordings

Authors: E. ABDELALEEM, *A. J. SEDERBERG;
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Abstract: Neural computation is nonlinear, yet the dominant tools for measuring statistical dependencies in neural populations are not. Mutual information (MI) is the natural measure: model-free, in bits, directly comparable across areas, conditions, and modalities. However, MI estimation from large populations has been intractable. Classical estimators fail beyond ~ 10 neurons/dimensions. Neural network-based (NN) estimators scale in principle but have lacked bias control, confidence intervals, and guards against overfitting, making them untrustworthy as scientific measurements.
Recent work by us and others established conditions for reliable, bias-corrected NN-MI estimation in high-dimensional regimes (Abdelaleem et al., 2025), and showed that the same MI(X;Y) calculation can be repurposed for intrinsic dimensionality estimation from learned embeddings (Gulati, Abdelaleem et al., 2026). Here we present NeuralMI, an open-source Python library packaging these advances for neuroscience. The core insight is that the same estimation procedure, applied with different inputs, answers a broad class of questions previously inaccessible to information theory at population scale.
We illustrate this across three analyses using publicly available recordings. Computing MI between random population halves as a function of embedding dimension, we identify where MI saturates as the population's intrinsic informational dimensionality; in large-scale V1 recordings (N ~ 10k neurons), this reveals dimensionality below 10 despite a power-law PCA eigenspectrum implying thousands, suggesting apparent high-dimensionality is a linear artifact. Extending the same estimator across brain areas, preliminary MI analysis between visual cortex and hippocampus across static and dynamic stimulation suggests hippocampal-cortical coupling is selectively elevated during temporally structured input. Applying it to neural-behavioral dependencies, preliminary conditional MI analysis of hippocampal population activity suggests that binary navigational direction (left vs. right) contributes approximately 1 additional bit beyond spatial position alone.
These examples represent a fraction of what NeuralMI enables. Reliable nonlinear MI estimation in absolute units, now tractable at the scale of modern neural recordings, transforms a broad class of previously inaccessible neuroscience questions into direct, comparable measurements. NeuralMI is available at https://github.com/eslam-abdelaleem/NeuralMI.

Disclosures: E. Abdelaleem: None. **A.J. Sederberg:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.11/CC9

Topic: E.06. Vision

Support: NIH Grant R01DC002390
NIH Grant R01DC018061
NIH Grant T32DC000023
NIH Grant T32GM136577
NSF CAREER Award 2340338

Title: Partitioning neural co-variability with a population overdispersion model

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Abstract: Trial-to-trial variability of neural responses has been linked to important aspects of neural computation and is essential for understanding how neuronal populations respond. While current overdispersion models treat each neuron's gain as independent of each other, this assumption fails to capture the network statistics of neuronal populations. As no existing model can capture overdispersed structured spiking gain-modulation across a neural population, network-level gain covariance remains largely unstudied.
We thus present the Poisson matrix-normal latent variable (PMNLV) model, which extends single-neuron overdispersion to neural populations by placing a matrix-normal prior over the latent gain with a Kronecker-factored covariance. We derive two complementary algorithms: a variational EM (VEM) with a matrix-normal posterior that recovers dense Kronecker factors without structural assumptions and a Kernel Tournament Method (KTM) that performs data-driven selection over a biologically motivated kernel dictionary and composite likelihood. Our methods were benchmarked against four other methods and scored on relative error to ground truth covariance and tuning curves.
On simulated data, both algorithms recover the neuronal and temporal covariance terms (<20% error) and tuning curves (<12% error). Applying VEM to Neuropixel recordings across four cortical regions of the mouse visual hierarchy, we demonstrate generalizability via predictive log-likelihood (PLL) validation and recover realistic single-neuron tuning curves. We replicate previous findings showing that single-neuron marginal variability changes little across cortical areas (LGd/VISp, p=3.03e-18, VISp/VISrl, p=1.02e-1, VISrl/VISam, p=7.80e-21). We then show that shared population co-variability, invisible to scalar summaries such as the Fano factor, peaks in primary visual cortex and declines in higher visual areas (LGd/VISp, p = 6.80e-8, VISp/VISrl, p=5.43e-2, VISrl/VISam, p=4.27e-2), consistent with functional connectivity studies. Lastly, we demonstrate that the neural activity and neuron noise subspaces are substantially misaligned (alignment index<0.6) across cortical areas, suggesting that shared gain covariance captures population structure distinct from stimulus-driven neural activity.

Disclosures: S. Thomas: None. **B.J. Zhu:** None. **K.E. Cullen:** None. **A. Charles:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.12/CC10

Topic: E.06. Vision

Support: NIH R01 EY025102

Title: Membrane potential fluctuations reflect population spiking in awake mouse visual cortex

Authors: *L. J. JENNINGS[1], R. T. O'SHEA[2], T. TAILLEFUMIER[3], N. J. PRIEBE[4];
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Abstract: The degree to which the activity of an aggregate population of spiking neurons is correlated with the membrane potential (V_m) fluctuations of a neuron in the same network is unknown. Previous work has shown that spike-count correlations between cortical neurons are weak, but paired intracellular recordings show that V_m-V_m fluctuations are highly correlated. Here we have simultaneously recorded large-scale population spiking activity and V_m in primary visual cortex (V1) using Neuropixels and whole-cell patch-clamp recordings in awake head-fixed mice. Based on measured cross-correlations, we find that the correlation between V_m and the summed activity of recorded population spiking is relatively modest, ranging from 0.1-0.25 (n = 14 recordings, n = 10 animals). Additionally, we find that this correlation is largely dominated by coherence in the low-frequency domain (0-10hz), suggesting that the correlated activity between population spiking and V_m is driven by slow, network-wide fluctuations. Given that correlated activity has been shown to depend on network state, we sought to determine how visually-evoked activity impacts measured population-V_m correlations. We find that the magnitude of the correlation is unaffected between spontaneous and visually-evoked conditions, but the timescale of the correlation between population spiking and V_m shifts higher during visual stimulation (spontaneous = 144.5ms, n = 14 recordings; visually-evoked = 92.8ms, n = 8 recordings, $p < 0.05$). When examining the relationship between V_m and individual units in our recorded populations, we find that high-firing rate units exhibit stronger correlations with V_m than units with low firing rates, but that unit-V_m correlations are Gaussian and weak on average (mean = 0.02, std = 0.02, n = 583 units, 14 recordings). These results suggest that population-V_m correlations emerge from the summed activity of the population, rather than specific subsets of neurons. To further examine this, we adapted a previously published conductance-based model to our dataset in which excitatory and inhibitory conductances are generated from a population of randomly connected presynaptic neurons with a prescribed degree and timescale of synchrony (Pattadkal et al., 2026). We find that when randomly subsampling from this population to mimic our recorded populations, population-V_m correlations are similar to those in our recorded dataset. In summary, our results suggest that measured correlations between spiking activity and V_m from neurons in the same network are moderate and emerge as a result of broadly distributed network activity rather than specific subpopulations of neurons.

Disclosures: L.J. Jennings: None. **R.T. O'Shea:** None. **T. Taillefumier:** None. **N.J. Priebe:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.13/CC11

Topic: E.06. Vision

Support: NIH Grant DP2 LM014268

Title: A hybrid V1 model for predicting visual percepts from cortical stimulation

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Abstract: Cortical visual prostheses aim to create visual percepts by directly stimulating visual cortex, but electrical stimulation does not map cleanly onto perception. Patient reports indicate that these percepts, or phosphenes, vary in size, brightness, shape, and spatial structure, while limited human implant data makes them difficult to predict. Here, we developed an exploratory, hybrid V1 model for predicting cortical phosphenes from biologically constrained population activity. We trained our model on natural images from the COCO dataset to approximate a learned mapping from V1 population responses to visual perception. The model uses a retinotopic V1 map with simulated cells assigned receptive field sizes, orientation tuning, and simple-to-complex response properties. Natural images were encoded with Gabor-like receptive fields and decoded into image space using the learned perceptual mapping. We then simulated focal stimulation of the cortical surface. The model produced localized, structured phosphene predictions whose size and intensity varied with electrode eccentricity, stimulation strength, and electrode size, consistent with qualitative trends reported in human stimulation studies. These results suggest that the structure of predicted phosphenes may depend on the interaction between biological V1 properties and downstream decoding assumptions. This framework provides a way to probe how cortical organization may shape prosthetic vision, and generates testable predictions for future implant studies.

Disclosures: H.L. Stone: None. **M. Beyeler:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.14/CC12

Topic: E.06. Vision

Support: IMPRS-IS (International Max Planck Research School for Intelligent Systems)
BMFTR Grant FKZ 01GQ2107
Volkswagen Foundation Grant ZN4257
ERC Grant ERC-2022-STG NEURACT 101076710
HFRI Grant Agreement 4049
HFRI Grant Agreement 016552
Marie Skłodowska-Curie Actions Grant 101025482
ERC Grant Agreement 101041669
ERC Grant Agreement 101117156
NIH Grant R01EY026927

NSF Grant IIS-2113173
DARPA Contract N66001-19-C-4020
DARPA Contract N66001-17-C-4002
Amaranth Foundation (Enigma Project)
Stanford VPUE Undergraduate Research Major Grant

Title: Dual feature selectivity enables bidirectional coding in visual cortical neurons

Authors: *G. ACA[1], K. FRANKE[6], N. KARANTZAS[2], K. F. WILLEKE[3], M. DIAMANTAKI[7], K. RAMAKRISHNAN[8], P. ELUMALAI[9], K. RESTIVO[10], P. FAHEY[4], C. NEALLEY[11], S. S. PATEL[5], A. S. ECKER[12], E. Y. WALKER[10], F. H. SINZ[13], A. S. TOLIAS[5]; [1]Symbolic Systems, Stanford Univ., Stanford, CA; [2]Ophthalmology, Stanford Univ., Menlo Park, CA; [3]Cognitive Neurol., [4]Dept. of Neurosci., [5]Ophthalmology, Stanford Univ., Stanford, CA; [6]Stanford Sch. of Med., Palo Alto, CA; [7]IMBB - FORTH, Heraklion, Greece; [8]Univ. of Amsterdam, Amsterdam, Netherlands; [9]Inst. of Computer Sci. and Campus Inst. Data Science, Univ. of Göttingen, Göttingen, Germany; [10]Baylor Col. of Med., Houston, TX; [11]Dept. of Ophthalmology, Byers Eye Institute, Stanford Univ. Sch. of Med., Stanford, CA; [12]Ctr. For Integrative Neurosci., Tuebingen, Germany; [13]Lower Saxony Ctr. for AI and Causal Methods in Med., Hanover, Germany

Abstract: Sensory neurons are traditionally viewed as feature detectors that respond with an increase in firing rate to preferred stimuli while remaining unresponsive to others. Here, we identify a dual-feature encoding strategy in macaque visual cortex, wherein many neurons in areas V1 and V4 are selectively tuned to two distinct visual features—one that enhances and one that suppresses activity—around an elevated baseline firing rate. By combining neuronal recordings with functional digital twin models—deep learning-based predictive models of biological neurons—we were able to systematically identify each neuron's preferred and non-preferred features. These feature pairs served as anchors for a continuous, low-dimensional axis in natural image similarity space, along which neuronal activity varied approximately linearly. Within a single visual area, visual features that strongly or weakly activated individual neurons also had a high probability of modulating the activity of other neurons, suggesting a shared feature selectivity across the population that structures stimulus encoding. We show that this encoding strategy is conserved across species, present in both primary and lateral visual areas of mouse cortex. Dual-feature selectivity is consistent with recent anatomical evidence for feature-specific inhibitory connectivity, complementing the feature-detector principle through circuit mechanisms in which selective excitation and inhibition may together enhance the representational capacity of the neuronal population.

Disclosures: G. Aca: None. **K. Franke:** None. **N. Karantzas:** None. **K.F. Willeke:** None. **M. Diamantaki:** None. **K. Ramakrishnan:** None. **P. Elumalai:** None. **K. Restivo:** None. **P. Fahey:** None. **C. Nealley:** None. **S.S. Patel:** None. **A.S. Ecker:** None. **E.Y. Walker:** None. **F.H. Sinz:** None. **A.S. Tolias:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.15/CC13

Topic: E.06. Vision

Support: The Scientific and Technological Research Council of Turkiye, Grant 225K067

Title: Resting-State Network Organization in Migraine: Contributions of Theta Connectivity and Intrinsic Alpha Dynamics

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Abstract: Migraine is associated with dysfunctional sensory processing even in the interictal period, such as increased susceptibility, cortical hyperresponsivity, and reduced adaptivity loss to repeated sensory exposure. Although these alterations are often examined in the sensory domains, less is known about large-scale resting-state network topology. We examined whether migraine is associated with altered resting-state connectivity, focusing on fronto-occipital coupling, and whether intrinsic alpha dynamics explain variability beyond diagnosis. Participants completed equivalent-noise visual tasks. Resting-state EEG was recorded during eyes-open and eyes-closed conditions before and after the tasks in interictal patients with episodic migraine without aura and healthy non-headache controls. Debiased weighted phase lag index (wPLI) connectivity was computed within frontal, occipital, parietal, and fronto-occipital ROIs and small-world organization was assessed on connectivity matrices. Individual alpha peak frequency (IAF) was estimated per-subject from occipital channels to define subject-specific alpha bands. Behaviorally, migraine patients showed impaired performance and reduced visual sensitivity, reflected in elevated internal noise estimates. They also showed higher parietal theta connectivity and lower IAF than controls (9.8 vs. 10.4 Hz), suggesting slower intrinsic alpha dynamics. Fronto-occipital low-alpha connectivity was not distinguished by diagnosis. Instead, IAF was lower in migraine patients and predicted fronto-occipital, occipital, and frontal coupling strength across all participants, whereas parietal connectivity showed no such relationship. Correspondingly, low-alpha small-world index was positively correlated with IAF, such that subjects with slower alpha dynamics showed less organized network topology. Migraine patients additionally exhibited elevated parietal theta connectivity. Together, these results indicate altered resting-state organization across posterior and fronto-occipital networks, and suggest that intrinsic alpha dynamics contribute to network-level connectivity variability in migraine beyond what diagnosis alone captures.

Disclosures: I. Akdogan: None. **S. Koc Yilmaz:** None. **I. Guzel:** None. **Ö. Akgün:** None. **D. Vuralli:** None. **H. Bolay:** None. **H. Kafaligonul:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.16/CC14

Topic: E.06. Vision

Support: STI2030-Major Projects Grant 2022ZD0204600

Title: Population orientation coding improves with stimulus contrast in macaque V1

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Abstract: Orientation selectivity of individual V1 neurons in macaque V1 are largely contrast-invariant (Alitto & Usrey, 2004), yet behavioral orientation discrimination improves markedly with increasing contrast. This discrepancy suggests that contrast-dependent enhancement of orientation coding may arise at the population level. To examine this possibility, we used two-photon calcium imaging to record the responses of large samples of V1 neurons in four awake, fixating macaques. At single-neuron level, orientation tuning bandwidth actually showed a small but significant increase with stimulus contrast (0.47 deg per octave, $p = 0.007$). However, the Fano factor decreased significantly (−0.091 per octave, $p < 0.001$), suggesting less response variability at higher contrast.To examine population orientation representations, we applied multidimensional scaling (MDS) to population responses and quantified pairwise Euclidean distances between orientations in a six-dimensional representational space. Mean adjacent-orientation MDS distance increased monotonically with contrast (0.031 per octave, $p < 0.001$). Consistent with this geometric expansion, population orientation-decoding (PLS regression with circular labels) progressively improved, with mean angular error decrease at a speed of −0.42° per octave ($p = 0.001$). Thus, increasing stimulus contrast enhanced V1 orientation encoding and decoding at the population level, in addition to reduced Fano factor, despite increasing tuning bandwidth at single-neuron level.Our previous work has revealed V1 neurons showing different subtypes of neuronal contrast response functions (CRFs), including Low-threshold/Steep-slope, High-threshold/Steep-slope, Medium-threshold/Steep-slope, Low-threshold/Shallow-slope, and Medium-threshold/Shallow-slope subtypes. Restricting the MDS analysis to each subtype revealed subtype-specific patterns of orientation manifold expansion across contrasts. Particularly, Low-threshold/Steep-slope neurons showed the most rapid manifold expansion at low contrast levels, but a contraction at the highest contrast, and High-threshold/Steep-slope neurons exhibited the steepest expansion at high contrast. These results indicate that population-level orientation coding is not uniform but reflects heterogeneous contributions from subpopulations showing distinct CRFs.

Disclosures: C. Chen: None. **S. Tang:** None. **C. Yu:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.17/CC15

Topic: E.06. Vision

Support: Wellcome Trust/DBT India Alliance Senior fellowship IA/S/18/2/504003
Institute of Eminence (IoE)
Pratiksha Trust (Project AMRIT; IISc-PT-4720-2026)
Senior Research Fellowship (SRF), Pratiksha BCD Initiative

Title: Predicting responses to images using microelectrodes (PRIME)

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Abstract: Traditional neuroscience experiments have often overlooked colored natural image stimuli, in favor of simpler ones like grayscale images or gratings. This rich class of stimuli has consequences for real-world vision, where features like depth and coloration inform decisions. Studies have found individual features in images to modulate neural responses, but their relative contribution remains poorly understood. To bridge this gap, we built a model combining image-computable features known to correlate with neural activity from the primary visual cortex (V1). We obtained microelectrode (local field potential (LFP) and spike) data from two bonnet macaques (*Macaca radiata*) trained to passively fixate for 1.6s on images (64 color + 64 grayscale). We extracted 45 features, encompassing luma (grayscale) and chroma (color) channel information, for each image and electrode receptive field (RF) pair. In addition, we investigated a special feature that measures the predictability (P) of RF center pixels from the surround. We found that features based on luma and chroma channels of images target distinct regions in time-frequency space. Luma features were correlated with broadband gamma (aperiodic, 30-80Hz) but less with low frequencies (alpha/beta). Hue and saturation (ScosH), a chroma feature, correlated strongly with narrow-band gamma (periodic, 40-60 Hz). Contrary to previous claims, P was only weakly correlated with gamma bands and low-frequency power. Finally, we used L2 regularized multiple regression to predict the overall gamma (30-80Hz) response to both image classes. We obtained comparable (≈0.75) correlations for both grayscale and color image classes across monkeys, with roughly equal contributions from luma and chroma features in the latter. Though adding P did not improve this result, its dependence on surround information has led us to investigate other surround-computable features and lower frequencies, where they may serve as feedback signals. So far, our results show that features inside the RF of color images can predict the gamma response, supporting its role as a feedforward signal.

Disclosures: S.S. Pai: None. **S. Ray:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.18/CC16

Topic: E.06. Vision

Support: NIH NINDS U24-NS140384
NIH NINDS UM1-NS132207

Title: Retinotopic structural connectivity reveals organizing principles of the human visual connectome

Authors: *G. AMOROSINO[1], B. CARON[1], J. KWON[1], M. CARRASCO[2], R. REID[3], C. LENGLET[4], J. ZIMMERMANN[5], E. S. YACOUB[6], K. UGURBIL[7], S. R. HEILBRONNER[8], F. PESTILLI[1];
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Abstract: The human visual cortex systematically maps the spatial organization of the visual environment through retinotopic representations. Yet, the structural wiring that connects corresponding visual field representations across cortical areas remains largely unknown. Existing tractography studies have primarily characterized connections between anatomical regions, rather than between cortical locations representing the same positions in visual space. Here, we introduce VISCONN, an automated framework that combines diffusion MRI tractography with anatomically predicted retinotopic maps to reconstruct visual pathways by eccentricity and polar angle. We applied VISCONN to diffusion MRI data from more than 1,700 participants aged 2 to 88 years across the Human Connectome Project, Pediatric Imaging, Neurocognition, and Genetics, and Cambridge Centre for Ageing and Neuroscience datasets. We first tested whether human visual connectivity follows a retinotopic wiring principle, whereby cortical locations representing similar visual field positions preferentially connect. Across independent datasets, connections between early visual areas were strongest between homologous eccentricity representations and consistently declined with increasing visual field separation, revealing a statistically robust, spatially specific like-to-like organization. We next asked whether this retinotopic wiring reflects known asymmetries in visual perception. Connectivity within early visual cortex was stronger along the horizontal than vertical meridian and stronger in the lower than upper visual field, matching established horizontal-vertical and vertical-meridian perceptual asymmetries. These effects were absent in connections between visual cortex and the rest of the brain, indicating that visual field asymmetries are expressed primarily in local visual network architecture. Finally, we generated a population-level

retinotopic connectivity template from more than 160 million streamlines, enabling recovery of visual pathways when individual tractography is incomplete. Together, these findings show that human visual connectivity is organized in the coordinate system of visual space and provide a framework for linking anatomical wiring to visual perception across the lifespan.

Disclosures: G. Amorosino: None. **B. Caron:** None. **J. Kwon:** None. **M. Carrasco:** None. **C. Lenglet:** None. **J. Zimmermann:** None. **E.S. Yacoub:** None. **K. Ugurbil:** None. **S.R. Heilbronner:** None. **F. Pestilli:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.19/CC17

Topic: E.06. Vision

Support: NIH Grant R00EY031795
McDonnell Center for Systems Neurosci ence /Small Grants Program
NIH Grant R21EY036566

Title: Contextual Integration by Lightness Clusters in Area V4

Authors: *F. DIDEHVAR[1], R. VANSTIPHOUT[1,2], D. VIEIRA[1], T. P. FRANKEN[1];
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Abstract: The lightness of a surface is poorly predicted by its luminance, and instead strongly determined by visual context. The underlying neural process of context integration is poorly understood. Low-level theories propose a contrast-like computation, whereas mid-level theories propose that the visual system parses scenes into regions of approximately constant illumination, which then guide the computation of lightness. We recently identified "lightness clusters" in macaque visual cortical Area V4 — columns of neurons that show a net lightness bias in their representation of the local luminance (Didehvar et al., 2025). Here, we investigate how lightness clusters integrate visual context.We recorded from single- and multiunits in V4 of one macaque using Neuropixels probes. After mapping the classical receptive fields (cRFs), we presented checkerboard scenes with spatially varying illumination, to identify lightness clusters as in our recent work. We then presented Noisy Argyle scenes (Kim et al., 2018; more than 5000 unique scenes per session) while the animal was fixating a small target. These scenes are derived from the Argyle illusion, in which alternating illumination bands have a strong effect on surface lightness (Adelson, 2000). Noisy Argyle scenes were generated by adding an independent sample of Gaussian luminance noise to distinct scene elements, but not to the square in which the cRFs were positioned. Spike-triggered averaging revealed individual units that were mostly influenced by scene elements in the illumination band that contained the cRFs, and mostly close to the cRFs. To investigate if this pattern is relevant at the population level, we developed a cross-condition decoding approach. We trained random forest regressors on population spike

counts to checkerboard responses to decode the luminance in the cRFs. We then used these decoders to decode luminance from the Noisy Argyle responses. We identified the scene elements that significantly influenced the decoded luminance by comparing the groups of scenes with resp. the lowest and the highest decoded luminance. In lightness clusters we find that these scene elements were clustered similar to the pattern of single units (permutation test $p<0.05$, 2 penetrations). In a third penetration which was not a lightness cluster, the pattern did not respect the illumination borders. Together our data suggest that the representation of luminance in lightness clusters is mostly influenced by patches in the same illumination band (as predicted by mid-level theories), but dependent on distance (as predicted by low-level theories), consistent with human psychophysics (Kim et al., 2018).

Disclosures: F. Didehvar: None. **R. Vanstiphout:** None. **D. Vieira:** None. **T.P. Franken:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.20/CC18

Topic: E.06. Vision

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0204802)
National Natural Science Foundation of China (T2421004, 31930053)

Title: A Generalizable, Subject-Transferable Visual Brain-Computer Interface for Color and Orientation Decoding from Human Intracranial Recordings

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Abstract: Visual brain-computer interfaces (BCIs) offer a direct route to restoring and augmenting human sight, yet they remain far less mature than motor and speech BCIs. A central obstacle is the lack of large-scale, high-signal-to-noise intracranial recordings from human visual cortex, which has limited the development of decoders that are both accurate and transferable across individuals. Here we develop a generalizable visual BCI for decoding human visual perception from intracranial electroencephalography (iEEG), focusing on two fundamental dimensions of visual experience: color and orientation. We assembled, to our knowledge, the largest high-quality intracranial dataset of human visual perception to date, recording iEEG from 54 participants, of whom 46 passed quality control, yielding 1,198 visually responsive contacts. Participants viewed chromatic gratings spanning seven hues and four orientations, together with

an achromatic control. Using this resource, we developed PrismaNet, a compact neural decoder that achieved high-fidelity within-subject color decoding, with accuracy reaching 98.3%. Its internal geometry recapitulated the canonical hue circle, indicating that the model captures the perceptual structure of color rather than arbitrary stimulus labels. Decoding further approached its asymptotic performance using only two selective electrodes, approximately 200 ms of post-stimulus activity and around 300 training trials, defining a practical regime for real-time visual BCIs. To overcome the subject-specific bottleneck that has constrained clinical translation, we introduced a shared-core and subject-adapter architecture. After pretraining across source participants, the model transferred to new individuals with non-inferior accuracy and 2-3-fold faster convergence, substantially reducing calibration demands. The learned representation also generalized beyond trained stimuli, decoding untrained hues at finer color samplings and color imagery evoked by grayscale object cues. Together, these results establish a high-fidelity, subject-transferable and task-generalizable framework for visual BCIs, and provide a foundation for closed-loop visual neuroprostheses enabled by co-designed compute-in-memory hardware for real-time decoding and on-chip personalization.

Disclosures: S. Zhang: None. **G. Chen:** None. **R. Yang:** None. **Q. Wang:** None. **F. Fang:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.21/CC19

Topic: E.06. Vision

Support: NIH grant 1R21MH133097-01

Title: Mismatch Negativity in the visual Cortex

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Abstract: Mismatch negativity (MMN) is a widely used electrophysiological marker of sensory prediction and change detection, with translational relevance to neuropsychiatric disorders. Although MMN has been studied most extensively in audition, visual mismatch negativity (vMMN) is also well established. Classical oddball paradigms define MMN as the difference between responses to rare deviant stimuli and repeated standards. Most work has treated MMN as a scalar change in response magnitude, leaving unclear how adaptation and novelty are represented at the level of cortical population activity. Here, we investigated vMMN in mouse primary visual cortex (V1) as a high-dimensional population phenomenon. We performed 64-

channel silicon-probe recordings while mice viewed drifting gratings presented in oddball and control sequences. By comparing standard, deviant, and control responses in neural state space, we asked whether stimulus-specific adaptation (SSA) and novelty detection reflect shared or separable transformations of the V1 population code. We found that vMMN in V1 is multidimensional. Repeated oddball stimulation produced global adaptation of the sensory population code, expressed as a rotation of the visual stimulus manifold. SSA was concentrated within this stimulus manifold, consistent with a bottom-up sensory adaptation mechanism. In contrast, novelty-related activity emerged largely in an orthogonal off-manifold dimension. Within this off-stimulus manifold, deviant and standard responses were displaced from control responses in opposite directions: deviant stimuli produced a positive novelty component, whereas repeated standards produced a negative novelty component. Thus, novelty detection in V1 extends beyond classical deviant enhancement and includes bidirectional population displacements relative to control activity. Finally, optogenetic inhibition of anterior cingulate cortex projections to V1 preferentially reduced off-manifold novelty responses, supporting a role for top-down feedback in visual deviance processing. Together, these findings show that vMMN reflects distinct population transformations: global adaptation reshapes the sensory manifold, SSA acts within that manifold, and novelty signals emerge in an orthogonal dimension shaped by ACC feedback.

Disclosures: A. Vázquez: None. **S. Kim:** None. **R. Batista-Brito:** None. **L.L. Sjulson:** None.

Poster

PSTR231: Visual Cortex: Populations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR231.22/CC20

Topic: E.06. Vision

Support: NIH Grant 1ZIAEY000570-01
NSF Grant IIS1350990
NIH Grant R00EY032179

Title: State-dependent modulation is pronounced and heterogeneous in the primate visual cortex

Authors: *B. TALLURI[1], I. KANG[1], J. YATES[2], D. A. BUTTS[3], H. NIENBORG[1]; [1]NIH, Natl. Eye Inst. (NEI), Bethesda, MD; [2]Optometry, UC Berkeley, Berkeley, CA; [3]Dept. of Biol., Univ. of Maryland, Col. Park, College Park, MD

Abstract: Internal states like arousal have a pronounced influence on neuronal activity across the brain, and recent rodent studies revealed that their modulatory effects are not uniform across neuronal populations. Here, we hypothesized that primates show similar modulations with arousal and examined neuronal activity in macaque V1 and V2 areas while monitoring fluctuations in arousal. We recorded extracellular spiking activity from V1 (128 units) and V2 (204 units) areas of head-fixed macaques while manipulating internal states using different levels

of task engagement in blocks. Animals either performed a visual task to receive a reward (Task condition) or freely viewed with reward delivered at random times (No-Task condition). In both conditions, we drove neuronal activity by temporally modulating luminance of the entire display (full-field flashes). This stimulus ensured that the input to neuronal response fields was invariant to the animal's gaze position and hence comparable across the two conditions. Simultaneously measured physiological signals—pulse rate, respiration rate, and pupil amplitude—significantly differed between the two conditions, confirming experimental manipulation of arousal by task engagement. Units across both areas exhibited pronounced, characteristic modulations between the conditions: greater stimulus-driven activity, lower spike-count variability and smaller noise correlations in the Task than No-Task conditions. Notably, these modulations were larger in V1 than in V2: stimulus-triggered activity increased by 58% in V1 and 26% in V2; and pairwise spike-count correlations decreased from No-Task to Task, from 0.11 to 0.03 in V1, and from 0.23 to 0.18 in V2. Latent variable modelling further revealed two classes of units in V2, but not V1, showing lower or higher baseline activity in the Task compared to No-Task conditions. These two classes further showed quantitative differences in their arousal-related modulation of spike-count correlations and spike-count variability. Together, we identified pronounced arousal-related modulation in early visual cortex and differential modulation in V2, which may reflect the heterogeneous innervation of the neuromodulatory systems within and across the early visual areas in macaques.

Disclosures: B. Talluri: None. **I. Kang:** None. **J. Yates:** None. **D.A. Butts:** None. **H. Nienborg:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.01/CC21

Topic: F.02. Cerebellum

Title: The role of an RNA binding protein in mouse cerebellum

Authors: *C.-Y. TSAI, H.-S. HUANG;
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Abstract: <META NAME="author" CONTENT="蔡長祐">The role of an RNA binding protein in mouse cerebellumChang-Yu Tsai[1], Hsien-Sung Huang[1]1.Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei 10051, Taiwan.RNA-binding proteins are a group of proteins that play an essential role in RNA regulation by guiding RNA localization, binding to RNA to regulate its stability, and facilitating pre-mRNA alternative splicing for appropriate protein translation. In pervious study, we identified a mutation in specific RNA-binding protein, *GeneR*, in patients with neurodevelopmental disorders. Moreover, several clinical studies have revealed that the dysfunction of *GeneR* in humans has been linked to epilepsy, neurodevelopmental delay,

cognitive impairment, speech deficits, and other disorders. Furthermore, this GENER is highly expressed in the cerebral cortex, striatum, hippocampus, amygdala, and cerebellum. Several studies indicate that dysfunction of *GeneR* impairs specific learning behaviors, neurogenesis, and neural activity in specific brain regions. However, while these neuropsychiatric studies have focused on the cerebrum, very few have investigated the cerebellum. Although GENER plays an essential role in neural development and the maintenance of adult cerebral function, its function in the cerebellum remains poorly understood. To fully elucidate the impact of *GeneR* on cerebellar function, we evaluated cerebellar granule cell-specific knockout mice to determine the behavioral, morphological, and molecular impacts of GENER dysfunction in cerebellar granule cells. Our results reveal that the loss of GENER in the cerebellum significantly impairs motor-related behaviors, alters both cerebellar weight and structure, and induces specific alterations in molecular expression.

Disclosures: C. Tsai: None. **H. Huang:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.02/CC22

Topic: F.02. Cerebellum

Support: 5R01NS131646-03

Title: Population-level movement encoding dysfunction across the cerebellar cortical-nuclear axis in a mouse model of Ataxia-Telangiectasia

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[1]Neurol., The Lundquist Inst. at Harbor-UCLA, Torrance, CA; [2]Neurol., Lundquist Institute/UCLA, Torrance, CA

Abstract: Ataxia-Telangiectasia (AT) is a progressive neurodegenerative disorder caused by ATM kinase loss-of-function. Purkinje cell degeneration is established in aged AT mice, yet how surviving circuitry encodes movement transitions and propagates signals to deep cerebellar nuclei (DCN) remains unknown. Using 128-channel silicon probes in awake locomoting one-year-old AT knockout (EXP) and control (CTL) mice, we recorded 3,826 single units across cerebellar cortex (CTL n=1,027; EXP n=870) and DCN (CTL n=1,132; EXP n=797) during treadmill locomotion. EXP animals showed reduced locomotor speed in both cohorts ($p<0.05$; $p<0.01$), while overall firing rates were preserved across regions. Population PSTH analysis identified three movement-aligned classes, pre-onset activators, onset bursters, and onset pausers, present in comparable proportions across groups in both regions. In cerebellar cortex, EXP onset bursters showed higher-amplitude onset responses (~2.3 vs CTL ~1.9 z) with attenuated offset responses, dissociating onset and offset encoding within the same population. EXP onset pausers showed deeper onset suppression (~-2.0 vs CTL ~-1.2 z), pathological post-

offset rebound, and speed-invariant firing rate elevation across all locomotor speeds, indicating broad gain dysregulation in surviving cerebellar cortical neurons. In the DCN, overall onset responses were reduced in EXP (~1.0 vs CTL ~1.9 z), opposite in direction to cerebellar cortex. Pre-onset activators, the dominant DCN class (CTL 60%) lost their pre-movement excitatory ramp at both movement onset and offset, replaced by sustained suppression, indicating failure of anticipatory signaling at the cerebellar output stage. Paradoxically, EXP DCN onset bursters showed higher onset peaks (~2.5 vs CTL ~2.0 z) with preserved offset responses, suggesting compensatory circuit reorganization rather than uniform inhibitory drive changes. EXP DCN pausers showed paradoxical post-offset suppression (~-2.0 z), opposite to the post-offset rebound seen in cerebellar cortex pausers. These cell-type-specific disruptions of movement onset and offset encoding reveal structured population dynamics dysfunction across the cerebellar cortical-nuclear axis in late-stage AT, not explained by firing rate changes alone.

Disclosures: A. Singh: None. **P.J. Mathews:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.03/CC23

Topic: F.02. Cerebellum

Support: NIH R37-NS128416

Title: Effects of microstimulation of cerebellar oculomotor vermis on neural activities and behavior

Authors: *N. MOHAMMADREZAEI[1], J. DOOSTMOHAMMADI[1], R. SHADMEHR[2]; [2]Dept Biomed. Eng, [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The cerebellar oculomotor vermis contributes to the accuracy of saccadic eye movements through circuits in which climbing fiber inputs to Purkinje cells (PC) carry error signals that guide motor learning. Although electrical microstimulation of the cerebellar vermis has been known to alter saccade trajectories, the neural mechanisms through which cortical perturbation translates to behavioral changes remain poorly understood. To address this question, we combined intrasaccadic microstimulation of the oculomotor vermis (lobule VII) with extracellular recordings to characterize the local neural consequences of stimulation and their relationship to saccade kinematics. Biphasic high frequency stimulation pulses were delivered during the acceleration phase of primary saccades and continued until movement termination. Surprisingly, stimulation produced a robust suppression of PC simple spike firing that persisted for up to hundreds of milliseconds after the end of stimulation. Molecular layer interneurons were also suppressed during stimulation, demonstrating that the reduction in PC activity was unlikely to result from increased local inhibitory input. In contrast, stimulation was followed by a synchronized increase in complex spike (CS) activity which peaked at 17 ms after stimulation

offset. We had hypothesized that there would be a relationship between CS tuning of Pcells and their downstream effects on behavior. At stimulation sites, the population CS preferred direction was approximately 230°. Stimulation produced systematic shifts in saccade endpoints in a direction ~95° away from this population preference and was accompanied by an increase in saccade deceleration duration. Thus, the surprising result was that electrical stimulation produced concurrent suppression of PC simple spike activity and molecular layer interneurons. This suggests that the reduction in PC spiking at the soma is unlikely to be mediated by increased local GABAergic inhibition. Instead, it may reflect a direct effect of stimulation on neuronal excitability, such as depolarization block. Furthermore, the delayed and synchronized increase in CS activity may arise from recruitment of the nucleo-olivary pathway, consistent with mechanisms proposed in previous optogenetic studies. We hypothesize that microstimulation suppressed somatic spike generation while driving axonal activity, as reported during high frequency stimulation in basal ganglia. This results in Purkinje cell somatic suppression while axonal output remains activated. Such a mechanism could account for both the decrease in simple spike firing and the delayed increase in CS activity.

Disclosures: N. Mohammadrezaei: None. **J. Doostmohammadi:** None. **R. Shadmehr:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.04/CC24

Topic: F.02. Cerebellum

Support: NIH R37-NS128416

Title: Complex spikes in the cerebellar hemispheres during saccades

Authors: *E. A. TAECKENS[1], A. M. SHOUP[2], R. SHADMEHR[3];
[2]Biomed. Engin., [3]Dept Biomed. Eng, [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The climbing fiber input to the cerebellum plays an essential role in motor learning by inducing complex spikes (CS), which drive plasticity at parallel fiber - Purkinje cell (P-cell) synapses. Classic views suggest that complex spikes respond to motor errors, and that the resulting plasticity drives behavioral changes that reduce these errors. Recent work on the saccadic system has revealed important details of this error correction mechanism. Complex spike rates in the oculomotor vermis (OMV), a region that is necessary for accurate saccades, are strongly modulated as a function of the direction of visuomotor events. Moreover, the direction of the sensorimotor event that maximizes the CS rates corresponds to the P-cell's potent vector, i.e., the direction in which the eye moves when the P-cell is suppressed. This correspondence ensures that CS induced LTD reliably results in reduction of motor error. Thus, the climbing fiber input provides information about the downstream anatomical connections of individual P-cells. Critically, CS rates are at baseline for visuomotor events perpendicular to the P-cell's

potent vector, ensuring that on average no plasticity is induced for motor errors that the cell is incapable of influencing.The more lateral cerebellar regions adjacent to the OMV, referred to as the hemispheric oculomotor region, have also been shown to play a role in saccade control, but less is known about the climbing fiber inputs to these areas. We recorded from 105 P-cells in Lobule VII of the medial paravermis and 118 P-cells in the more lateral Lobule VII and found systematic differences compared to the vermis. The CS preferred directions for most cells in the paravermis and the hemispheres were ipsilateral, whereas in the vermis they were contralateral. Unlike the vermis, the CS rates were positively modulated for saccades perpendicular to the preferred direction, suggesting that their potent vectors did not linearly map to changes in eye movements. Additionally, CS modulation peaked after the saccade was already over, rather than at the beginning of the saccade or at the time of visual error, as typically occurs in the vermis. Finally, CS rates in the lateral regions were modulated even during unrewarded, task-irrelevant saccades, whereas CS rates in the vermis were only very weakly modulated during task-irrelevant saccades. These results suggest that the P-cells in the hemispheric oculomotor region may be subject to different learning rules than those in the oculomotor vermis, and they may contribute to different aspects of saccade control.

Disclosures: E.A. Taeckens: None. **A.M. Shoup:** None. **R. Shadmehr:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.05/CC25

Topic: F.02. Cerebellum

Support: NIH F31-NS14761
NIH R37-NS128416

Title: Synchronous spiking of inhibitory interneurons reduces the timing variance of downstream neurons

Authors: *A. N. VASSERMAN[1], M. FAKHARIAN[3], E. TAECKENS[2], A. SHOUP[1], R. SHADMEHR[2];
[1]Biomed. Engin., [2]Dept Biomed. Eng, Johns Hopkins Univ., Baltimore, MD; [3]Biomed. Engin., MIT, Cambridge, MA

Abstract: Neurons are classified as excitatory or inhibitory by their effect on postsynaptic targets, yet many inhibitory neurons electrically excite one another. In the cerebellar cortex, type 1 molecular layer interneurons (MLI1s) inhibit Purkinje cells (P-cells) via electrical (pinceau) and chemical (GABA) synapses while exciting each other through gap junctions, aligning some of their spikes to within 1 ms. What is gained when two MLI1s synchronously inhibit their target? We recorded from lobules VI-VII of the marmoset cerebellum during saccades using Neuropixels and Cambridge Neurotech probes, identified P-cells and putative MLI1s, and

clustered them into small networks (cliques) based on their short-latency spike interactions. Within these cliques, we isolated triplets in which two MLI1s converged onto a single P-cell (n = 10,451 triplets) and measured the jitter-corrected effect of the MLI1 pair on the P-cell's simple spikes as a function of the inter-MLI1 interval and the P-cell's instantaneous firing rate. A single MLI1 spike produced a bimodal suppression in the downstream P-cell. This suppression consisted of an early pinceau component (~0.4 ms) and a later GABA component (~1.3 ms), which was then followed by a post-inhibitory rebound beginning ~2.5 ms later. This effect was state-dependent: at higher P-cell firing rates both the suppression and the rebound were larger. When two MLI1s spiked within 1 ms of each other, their effects superposed, roughly doubling both the suppression and the rebound relative to a single spike. However, when the MLI1s spiked 2-4 ms apart, the later spike's inhibition collided with the former spike's rebound, producing interference and a partial cancellation of the inhibitory effect. We then measured the probability density of the timing of the P-cell's first spike following inhibition from a pair of upstream MLI1s. This density formed a peak around 3.5 ms, and as the MLI1 spikes became more synchronous, the peak sharpened. This effect was stronger for MLI1s that more strongly inhibited their downstream P-cell. Thus, production of synchronous MLI1 spikes resulted in improved precision of P-cell simple spikes, reducing their variance. Therefore, electrical coupling among inhibitory neurons promotes spike intervals that enhance constructive superposition while reducing destructive interference. This provides a means for the upstream inhibitory neurons to control spike-timing of the target neuron.

Disclosures: A.N. Vasserman: None. **M. Fakharian:** None. **E. Taeckens:** None. **A. Shoup:** None. **R. Shadmehr:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.06/CC26

Topic: F.02. Cerebellum

Support: RO1NS122741

Title: Cerebellar transcranial AC stimulation elicits phase-dependent changes in the Purkinje cell complex spike waveform.

Authors: *D. MOURRA[1], J. SLOANE[2], M. SAHIN[3], E. J. LANG[2];
[2]Neurosci., [1]New York University, Grossman Sch. of Med., New York, NY; [3]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ

Abstract: Cerebellar transcranial alternating current stimulation (ctACS) can improve motor learning and modulate cognitive and emotional processes, but the underlying cellular mechanisms of these actions remain poorly understood. Purkinje cell (PC) complex spikes (CSs) and their waveforms are important parameters that play a role in cerebellar synaptic plasticity.

Thus, we examined how ctACS alters CS waveform. We obtained extracellular recordings from PCs in anesthetized adult rats during ctACS (500 μA peak-to-peak, 0.5-50 Hz) and determined the effect of ctACS on the following parameters of CS waveform: the absolute area under the curve (AAUC) and the number and amplitude of spikelets.
While ctACS did not expand the normal range of these parameters, it did cause phase-dependent changes in their distribution within this range. For the AAUC, all frequencies were effective, but the highest percentage of PCs showed modulation during 1 Hz ctACS. Analysis of individual spikelet periods showed that 93.8% of PCs showed significant changes in at least one period. Phase-dependent changes in spikelet number and amplitude were consistent with those found for the AAUC. More PCs showed statistically significant modulation of spikelet amplitude than of the number of spikelets. However, for those PCs with significant modulation, the effect size was similar for both parameters. PC location also influenced the strength of the modulation, which was strongest for superficial PCs that were located at or near the crown of the lobules. Lastly, the CS waveform modulation was correlated with the strength of simple spike (SS) modulation in the same PC, though the frequency dependence of the CS waveform and SS firing rate modulations differed.
In sum, these results show that ctACS exerts strong, phase-dependent control over the CS waveform with a distinct frequency dependence from that of SS entrainment. This separation suggests that stimulation parameters such as phase and frequency could be adjusted to target CS signaling related to plasticity or SS activity linked to output.

Disclosures: D. Mourra: None. **J. Sloane:** None. **M. Sahin:** None. **E.J. Lang:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.07/CC27

Topic: F.02. Cerebellum

Title: Modular organisation of cerebellar contributions to cortical dynamics during goal-directed behaviour

Authors: *S. GANGULY, C. ARSLAN, E. HALLSWORTH, D. KOSTADINOV;
CDN, King's Col. London, London, United Kingdom

Abstract: Long-range circuits linking the neocortex and cerebellum are essential for goal-directed behaviour, yet their dynamic computational interactions remain poorly understood. Our goal is to determine how cerebellar output, reflecting internal model computations, shapes cortical dynamics and behaviour. To this end, we developed an approach to perturb cerebellar output in awake, head-fixed mice while recording cortical population activity in the forebrain. We co-express the calcium indicator jGCaMP8m and the red-shifted excitatory opsin ChRmine in cerebellar Purkinje cells (PCs), identify functional PC microzones by clustering temporally correlated PC dendrites, and use holographic two-photon stimulation to perturb microzone-

grouped Purkinje cell populations across cerebellar lobules while recording activity in the caudal forelimb area (CFA) of motor cortex using Neuropixels probes.This approach revealed several organizing principles of cerebello-cortical communication. First, activating GABAergic PC microzones does not simply suppress cortical activity: low-rate stimulation produces balanced activation and suppression, whereas higher-rate stimulation preferentially suppresses cortical firing. Second, cerebellar influence is highly specific: activating a single microzone can evoke opposing responses in neighbouring cortical neurons, while neighbouring microzones can exert opposing effects on individual cortical cells. Third, motor-related cerebellar regions preferentially influence functionally aligned cortical regions, with Lobule simplex stimulations more effectively altering CFA activity than stimulation of Lobule VI or Crus I.We are now performing simultaneous recordings from functionally coupled regions of the cerebellum and motor cortex in mice performing a directional reaching task in order to investigate the shared latent contributions of these brain regions to movement-specific computations. These recordings have identified direction-specific encoding in the cerebellum and cortex, and we are now modelling the functional relationship between these local circuit dynamics. Going forward, we plan to employ our perturbational approach to determine how task-encoding microzones influence cortical population activity and ultimately drive behaviour.

Disclosures: S. Ganguly: None. **C. Arslan:** None. **E. Hallsworth:** None. **D. Kostadinov:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.08/CC28

Topic: F.02. Cerebellum

Support: NSERC Discovery Grant (RGPIN-2023-05107)
CIHR PJT180635

Title: Synaptic connectivity of cerebellar mossy fibers to inhibitory Golgi cells is regulated by Cadherin-23

Authors: *B.-I. MOKE[1], M. GRAY[2], A. FEKETE[3], E. LIN[1], T. NGUYEN[4], W.-C. A. LEE[4], L.-Y. WANG[3], J. L. LEFEBVRE[3];
[1]Dept. of Mol. Genet., Univ. of Toronto, Toronto, ON, Canada; [2]Univ. of Western Ontario, London, ON, Canada; [3]Program in Neurosci. and Mental Hlth., Hosp. for Sick Children Res. Institute: SickKids Res. Inst., Toronto, ON, Canada; [4]F.M. Kirby Neurobio. Ctr., Harvard Med. Sch., Boston, MA

Abstract: Inhibitory interneurons consist of highly diverse and spatially intermingled cell types that form highly specific connectivity patterns to regulate neural signaling. To identify molecular determinants of interneuron connectivity, we combined lineage tracing with RNA-sequencing to

profile developing interneuron subtypes in the cerebellum. This analysis identified selective expression of the atypical cadherin, Cadherin-23 (Cdh23), in Golgi cell interneurons (GoCs), key inhibitory regulators of the input layer of the cerebellum. Cdh23 has well-documented functions in auditory hair cells and the retina. Human mutations in Cdh23 and its known binding partner, Protocadherin-15 (Pcdh15) cause Usher Syndrome, a deaf-blindness disorder with gait and balance issues. However, the function of Cdh23 has not been described in the brain. RNA-FISH experiments confirmed the expression of Cdh23 and Pcdh15 in GoCs but not in granule cells. Cdh23 is also prominent in precerebellar neurons, including pontine and other brainstem nuclei that convey multisensory information to the cerebellum through mossy fiber (MF) afferents. MFs form large presynaptic rosettes that synapse onto both inhibitory GoCs and excitatory granule cells (GrCs), providing a powerful system to study target-specific synaptic connectivity. Based on the expression of Cdh23 in MF afferents and GoCs, together with known adhesive interactions between Cdh23 and Pcdh15, we hypothesize that Cdh23 contributes to the specificity and function of MF synapses onto GoCs. Here, we define a role for Cdh23 in specifying the MF-GoC synapse. Using retrograde AAV labeling and Cdh23-fusion protein expression, we confirmed that *Cdh23* is expressed by mossy fiber afferents and Cdh23 proteins localize to presynaptic MF rosettes. *In vitro* hemi-synapse assays and *in vivo* overexpression experiments showed that ectopic Cdh23 expression is sufficient to recruit mossy fiber boutons, supporting a synaptogenic role. Analyses of *Cdh23* knockout and conditional mutant mice reveal that Cdh23 is necessary for normal structure and function of MF terminals. MFs lacking *Cdh23* developed enlarged rosettes compared to controls, and exhibit altered synaptic transmission onto GoCs, including a reduced paired-pulse ratio consistent with increased release probability. Together, these studies identify a novel role for Cdh23 in the brain, and suggest that Cdh23 helps organize synapse formation and transmission of projections neurons onto inhibitory versus excitatory target cells.

Disclosures: B. Moke: None. **M. Gray:** None. **A. Fekete:** None. **E. Lin:** None. **T. Nguyen:** None. **W.A. Lee:** None. **L. Wang:** None. **J.L. Lefebvre:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.09/CC29

Topic: F.02. Cerebellum

Support: NIH R35 NS116854

Title: Projections and physiological role of trigeminocerebellar and pontocerebellar mossy fibers in whisker-related sensorimotor integration

Authors: *T. ROSSI, I. M. RAMAN;
Northwestern Univ., Evanston, IL

Abstract: Sensorimotor signals are conveyed to the cerebellum by mossy fibers (MFs), which relay whisker tactile sensory signals from the principal (Pr5) and spinal interpolaris (Sp5i) trigeminal nuclei, and whisking motor-command-related signals from the pontine nuclei (Pn). MF terminals, known as rosettes, form synapses onto each of the 3-5 dendrites of every granule cell, raising the question of the extent to which synaptic input from sensory trigeminal and motor pontine nuclei remain separate or converge. Here, we first investigated the anatomical patterns of trigeminocerebellar and pontocerebellar MF innervation in whisker-related cerebellar regions, and then examined their physiological contribution to synaptically driven firing of Purkinje cells and cerebellar nuclei (CbN) in awake mice. Tactile MFs were identified by injection of AAV1.hSyn.hChR2(H134R)-eYFP in Pr5 or Sp5i. Both trigeminal nuclei projected largely ipsilaterally, primarily to crus II for Pr5-MFs (9 mice) and crus I for Sp5i-MFs (7 mice). Pontocerebellar MFs, labeled by bilateral injection of the virus into the Pn, were present at high density in all lobules (4 mice). Transsynaptic labeling by injection of AAV1.hSyn.Cre.WPRE.hGH into the vibrissa motor cortex and AAV5.hSyn.FLEX-rc[ChrimsonR-tdTomato] into the Pn revealed motor-related MFs primarily in crus I (3 mice). Rosettes terminating onto granule cells in crus I, crus II, and the paramedian lobule were imaged confocally in Gabra6-cre mice that had received a unilateral injection of AAV1.CAG.FLEX.tdTomato in crus I/II and AAV1.hSyn.ChR2.eYFP in both Pr5 and Sp5i. Most labeled granule cells (96/107) received one trigeminal MF, with some (11/107) receiving two MFs. Even with bilateral labeling of Pr5 and Sp5i, only in a single granule cell were all three dendrites contacted by trigeminal inputs, suggesting that other granule cells may receive multi-sensory or sensorimotor synaptic input. Finally, MFs were optogenetically activated during extracellular recordings from Purkinje or CbN cells in awake mice. Stimulating Pr5 or Sp5i-MFs evoked strong net inhibition of Purkinje cells (110 cells) and excitation/disinhibition of target CbN neurons (23 cells). By contrast, activating Pn-MFs elicited strong net increases in Purkinje cell firing (54 cells). The data reveal that feedforward synaptic inhibition (granule - molecular layer interneuron - Purkinje cell) is preferentially recruited by trigeminal but not pontine inputs. Thus, the properties of synaptic connections of specific microcircuits may shape the spiking patterns of Purkinje cells and cerebellar nuclei to integrate whisker-related sensory and motor information.

Disclosures: T. Rossi: None. **I.M. Raman:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.10/CC30

Topic: F.02. Cerebellum

Support: NIS R35 NS116854 (IMR)

Title: Regulation of synaptically evoked spiking in inferior olivary neurons by postsynaptic voltage

Authors: *Z. W. SULTAN[1], I. M. RAMAN[2];
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Abstract: Unpredicted sensory stimuli elicit action potentials in neurons of the inferior olive (IO) that reliably evoke complex spikes in cerebellar Purkinje neurons, signaling the onset of learned sequences and instructing plasticity. Despite high levels of sensory input in most environments, IO spikes occur only at ~1.5 spikes/s, raising the question of what factors regulate synaptically driven IO spiking. Here, we tested how excitatory inputs from neurons of the mouse mesodiencephalic junction (MDJ) regulate the firing of IO neurons. In acute midbrain slices at 33-35°C from P35-P58 mice, retrogradely labeled, IO-projecting MDJ neurons fired spontaneously at 30 ± 13 Hz (n=10) with sustained rates reaching ~100 Hz for 0.5 s. Such rapid firing suggests that presynaptic and/or postsynaptic factors must strongly regulate IO spike probability. To estimate the strength of MDJ excitation to IO, we virally expressed ChR2 in the MDJ. IO neurons were then voltage-clamped near E_{Cl} (-70 mV) in brainstem slices (P35-P46), and EPSCs were evoked by stimulating MDJ terminals with a range of light intensities. Peak EPSCs ranged from -25 pA to >1 nA (n = 23, mean -412 pA with the maximal stimulus) and were consistent with ~10-20 afferents per cell. In current-clamped IO cells, the efficacy of MDJ afferents to elicit spikes depended strongly on pre-spike voltage. With maximal stimulation, the spike probability was 95 ± 15% when IO cells rested at -60 mV, but fell to 48 ± 34% at -70 mV and 19 ± 19% at -80 mV (n = 16 cells). Restricting analysis to cells with maximal EPSCs of -0.2 to -0.4 nA (~3-6 nS, n = 8) revealed spike probabilities of 98% at -60 mV, 51% at -70 mV and 15% at -80 mV. Consistent with a role for A-current in regulating spiking, the Kv4-specific blocker AmmTx3 could nearly fully abolish this voltage dependence. We then tested how electrotonic coupling affects voltage-dependent spike probability. ChR2 was virally expressed directly in IO cells, and cells were depolarized with either diffuse (widefield) or focal (~30 µm diameter) illumination that included the ~15 µm soma and proximal dendrites. With focal illumination, the probability of directly evoked spiking was 87% at -60 mV, but fell to 47% at -70 mV, and 15% at -80 mV (n = 13 cells), again consistent with strong voltage-dependence. With diffuse illumination in the same cells, however, spike probability was 100% at -60 mV as well as at -70 mV, and remained at 77% at -80 mV. The increased spiking with diffuse stimulation was consistent with a network contribution from gap junctional coupling. The data suggest that MDJ-driven IO spiking is likely gated by spatial summation, strongly voltage-dependent Kv4 currents, and electrotonic coupling.

Disclosures: Z.W. Sultan: None. **I.M. Raman:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.11/DD1

Topic: F.02. Cerebellum

Support: NIH Grant 25B5315

Title: Outcome probability signals in the cerebelloolivary circuit stabilize motor control

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Abstract: Cerebellar control of movement has been the subject of intense circuit-level investigation, with debates emerging around the tuning of instructive signals from the inferior olive (IO) that drive learning. While classical studies identify complex spike (CS) responses to motor error, an emerging body of work also identifies CS tuning to reward and reward expectation. The experimental paradigms associated with these distinct conclusions tend to be distinct, however, raising the question of whether CS signal reward expectation or errors during a dexterous movement to achieve a reward - a behavior with both motor control and reward outcome. We measured CS and associated cell types within the cerebelloolivary loop as mice performed reach-to-grasp movements to obtain food pellets using acute neuropixels probes. CSs reliably occurred around movement onset, and the probability of these onset signals scaled with recent success history: The earliest and largest signals (firing amplitude= 2.8 sp/s at 0.5 s before reach endpoint) occurred when success rates were highest, while after a string of failures, early CS were less prevalent (1.5 sp/s at 0.5 s prior to reach end). To determine how the cerebellum may contribute to regulating these signals, we built a classifier based on optotagged nucleoolivary (NO; n=129 units) and nuclear premotor neurons (n=50 units) to identify NO subpopulation across all recording sessions (accuracy=97%). Time-shifted CS signals were accompanied by temporally scaled NO activity: NO neurons fired earliest during strings of successes and latest during strings of failures, trailing the early CS signals under these conditions. To investigate the causal role of the NO pathway on learning, we performed optogenetic suppression experiments using soma-targeted GtACR2. When we inactivated NO neurons on successful trials - i.e. those associated with higher NO activity in control conditions - we found that the success rate in the n+1 trials were reduced by 13% relative to baseline ($p<0.01$; 8 mice). This reduction in success was associated with changes in reach kinematics, specifically target undershoot (0.5 mm decrease, $p<0.01$). We propose that by suppressing NO signaling on successful trials, we promote signals that drive movement variability that reduces next trial success likelihood. These data place cerebellar NO neurons in a position to regulate IO spiking to enforce appropriate pairing of motor commands and success likelihood.

Disclosures: A. Nashef: None. **C. Dobrott:** None. **D. Calame:** None. **J.M. Christie:** None. **A.L. Person:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.12/DD2

Topic: F.02. Cerebellum

Support: 1R01MH139606-01A1

Title: Aligned use of super-resolution STED microscopy and spatial transcriptomics to study human cerebellar synapses

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Abstract: Synapses are the fundamental building blocks of neuronal communication, yet there is remarkably little data directly quantifying the structure of synapses in intact human brain tissue. Here, we demonstrate the capability with super-resolution STED microscopy to reveal the nanostructure of thousands of synapses in archival human brain tissue. Moreover, we developed protocols to couple STED microscopy with cellular-resolution spatial transcriptomics to characterize the relationships between transcriptomic and synaptic variation across mesoscale imaging areas. Applying these approaches to characterize the diversity of synapses in the human cerebellum, we designed a multi-modal spatial and imaging pipeline to examine the abundance and nanostructure of excitatory synapses within the cerebellar cortex, while also gaining transcriptional insight into any given larger regions-of-interest (ROIs) utilizing spatial transcriptomics. We sequenced and imaged region-matched (vermal and lateral) post-mortem donor cerebellum of adult individuals (n = 3), using the Takara Seeker (10um) and the Takara Trekker (25um) for spatial transcriptomics and stimulated emission depletion (STED) microscopy for synapse imaging. By performing these complementary techniques on adjacent tissue sections, we produced two correlated spatial-STED maps. We evaluated the spatial distribution of neuronal subtypes, and identified spatial clusters corresponded to the granule, Purkinje, and molecular layers with the expected distribution of cell type markers. We identified structural properties distinguishing the three major types of excitatory synapses in the human cerebellum - climbing fibers, parallel fibers, and mossy fibers — and systematically characterize variation between vermal and lateral sub-regions of the cerebellar cortex. Further, we successfully aligned our spatial dataset with STED images of excitatory synapses across the cortex at 70 nm resolution in the adjacent tissue section using both STED and confocal validated antibodies and nanobodies. We measured the abundance of PSD-95, a postsynaptic receptor scaffold, and Bassoon, a presynaptic vesicle release protein, across the cortex, and discovered PSD subtypes that correspond to distance from the Purkinje cell layer. With the aim of creating a benchmark for the qualifications of healthy synaptic characteristics, we can use our pipeline to study the changes in idiopathic and genetic variants of autism spectrum disorders (ASDs) in human cerebellar cortices.

Disclosures: A. Biswas: None. **A. Wiltse:** None. **S.A. Ament:** None. **T.A. Blanpied:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.13/DD3

Topic: F.02. Cerebellum

Support: Simons Foundation Autism Research Initiative Bridge to Independence Award
UTSW O'Donnell Brain Institute Sprouts Grant Program

Title: Precision fMRI reveals face regions in the cerebellum

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Abstract: Faces are a strong social signal. Decades of neuroimaging research have identified areas that are selectively responsive to faces, such as the fusiform (FFA) and the occipital (OFA) face areas. These regions form a face-processing network that extends to temporal and frontal regions in the human neocortex. Importantly, while subcortical structures such as the cerebellum are strongly involved in high-level perceptual and cognitive functions, such as social cognition, language, working memory, and even retinotopic representations, no prior studies have investigated whether the cerebellum also contributes to face processing. Here, using a precision fMRI approach, we investigated whether the face-processing areas can be localized in the cerebellum.

We first examined cerebellar activation for faces from a dataset (n=25 adults) that used repetition suppression to engage stimulus-specific regions. We identified several face-responsive regions in the cerebellum - particularly in medial posterior cerebellar regions. Amongst these regions, a cluster in the left cerebellum-spanning medial Crus I/II/VIIb/VIIIa was highly selective for faces (i.e., responds more to faces than to other visual categories such as objects and visual words). We replicated these findings in several other datasets, from different face-related tasks, in 977 people from the Human Connectome project, and in 10 deeply-sampled individuals from the Midnight Scan Club dataset. We then found that cerebellar face regions are already present in infants and visible in non-human primates, indicating that cerebellar face specialization emerges early in development and across species. Finally, we examined responses to faces in clinical populations such as autistic adults (n=28) and individuals with developmental prosopagnosia (n=28). In both groups, cerebellar face regions showed reduced selectivity. In summary, our results demonstrate that face-selective areas can be localized in the cerebellum. This finding suggests that the existing neocortical face-selective network is only part of the face-processing system in the human brain, with cerebellar areas contributing an essential element to the more comprehensive face-processing network.

Disclosures: B. Wang: None. **A. Joshi:** None. **A. Desai:** None. **I. Abenes:** None. **J. Guo:** None. **A.M. D'Mello:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.14/DD4

Topic: F.02. Cerebellum

Support: UT Southwestern OBI Sprouts Grant
Simons Foundation Bridge to Independence Award
UT Southwestern CTSA Program CTSA-TPP-YR4-D-002
Once Upon a Time Foundation - Raynor Cerebellum Project

Title: Early cerebellar damage disrupts cortical growth, whole-brain functional networks, and cognitive outcomes

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Abstract: Developmental diaschisis refers to the idea that abnormalities or injury in one brain region during development can have downstream effects on the maturation and function of other anatomically distant brain regions that are connected to it. Prior work has found that damage to the cerebellum can result in atypical structure of the cerebral cortex including contralateral cortical volume reductions following cerebellar hypoplasia, dysgenesis, and/or hemorrhaging. Most prior research has used structural MRI to investigate diaschisis in individuals with cerebellar damage. However, there is minimal research combining multimodal (structural and functional) neuroimaging and deep behavioral phenotyping to more precisely characterize the effects of cerebellar damage during critical neurocognitive developmental periods. Here, we deeply phenotype a group of n=7 typically-developing (TD) adults and n=7 adults with early cerebellar damage (tumor resection at 3-6 yrs of age) to characterize long-term structural, functional, and neurocognitive outcomes. Cognitive abilities were characterized with a comprehensive neuropsychological battery, and structural and precision functional MRI was collected in all participants. We found that individuals with early cerebellar damage showed significant decreases in gray and white matter volume across all cortical lobes, with some preliminary evidence that lateralized cerebellar damage had the greatest impact on structural maturation of cortical association regions. Brain-behavior correlations indicated that lower cortical gray matter volume was associated with worse cognitive performance across multiple domains including reading, executive function, and language. Functional networks were also disrupted. Resting-state fMRI analyses demonstrated altered connectivity in cerebello-thalamo-cortical circuits in cerebellar patients. Our findings provide additional evidence that cerebellar insult during sensitive periods in development affects the growth of cortical areas with impacts on neurocognitive outcomes.

Disclosures: M.A. Blanco: None. **B. Wang:** None. **K. Haliru:** None. **A.M. D'Mello:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.15/DD5

Topic: F.02. Cerebellum

Support: NIH R35NS127248-04
NIH R00NS121274-04

Title: Serotonin Modulation in the Cerebellar Cortex in Health and Disease: Spinocerebellar Ataxia Type 1 (SCA1) and Temporal Lobe Epilepsy (TLE)

Authors: *C. CHAU[1], H. T. ORR[2], M. L. STRENG[3];
[1]Univ. of Minnesota Grad. Program In Neurosci., Minneapolis, CA; [2]Dept. of Lab. Med. and Pathology, [3]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Serotonergic fibers are the third largest afferent input to the cerebellum. Despite this rich serotonergic innervation, the roles of serotonin (5-HT) signaling in cerebellar function or its alterations in pathology are poorly understood. Early clinical studies treating cerebellar ataxia with serotonergic drugs suggest that 5-HT can contribute to motor coordination through the modulation of Purkinje cell activity. However, little is known regarding the spatiotemporal properties of 5-HT signaling in the cerebellum during motor control in vivo. A recently developed cerebellar wide-field imaging technique with a G-protein-coupled receptor (GPCR)-activation-based 5-HT ($GRAB_{5\text{-}HT}$) sensor provides the ability to interrogate the spatiotemporal properties of 5-HT signaling at the mesoscale level during awake behaviors. We found that 5-HT release onto Purkinje cells is dynamic, such that 5-HT signaling is dependent upon timing of motor preparation and execution. As a monoamine neurotransmitter, 5-HT has the ability to bind to various 5-HT receptors to modulate neuronal activity. These receptors have been targeted to treat neurological disorders that involve the cerebellum, such as Spinocerebellar Ataxia Type 1 (SCA1) and Temporal lobe epilepsy (TLE). However, the expression of these 5-HT receptors has not been extensively characterized in the cerebellum. Our immunohistochemistry data indicates that healthy animals heterogeneously express 5-HT receptor 1a ($5\text{-}HT_{1A}$) across lobules of the cerebellum. In the unilateral intrahippocampal kainic acid model of TLE, chronically epileptic mice exhibit decreased $5\text{-}HT_{1A}$ expression throughout the cerebellar cortex. Similarly, in a SCA1 mouse model, RNA sequencing data show decreased expression of $5\text{-}HT_{1B}$ in the cerebellum. Our ongoing work is interrogating how 5-HT signaling dynamics are altered during spontaneous hippocampal epileptiform activity in TLE, progression of SCA1 pathology, and whether these alterations correlate with changes in 5-HT receptor expression. All experiments ensure scientific rigor by including both sexes, conducting power analyses, and blinded analysis.

Disclosures: C. Chau: None. **H.T. Orr:** None. **M.L. Streng:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.16/DD6

Topic: F.02. Cerebellum

Support: KAKENHI 23K24714
KAKENHI 23K18257

Title: Neural circuit switching in the motor regulatory system: Early forced limb use promotes recovery via the cerebello-rubral tract after intracerebral hemorrhage

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Abstract: We have shown that the forced limbuse (FLU) following intracerebral hemorrhage (ICH) results in functional recovery, linked to a shift from the cortico-spinal tract to the cortico-rubral tract. However, it is still uncertain whether this transition also implicates the cerebellum within the motor regulatory system. To analyze the changes in the system caused by FLU, we focused on the cerebellar output system from the cerebellar lateral nucleus (Lat) to the parvocellular red nucleus (RNp) (cerebello-rubral tract: CRT). We evaluated upper limb function by silencing this tract using the DREADD system. AAV-DJ-EF1a-DIO-hM4D(Gi)-mCherry and FuG-E-MSCV-Cre were injected into the Lat and the RNp, respectively. The administration of clozapine-N-oxide (CNO) to block the CRT significantly decreased the success rate. However, CNO did not influence the success rate in normal animals, indicating a relationship between CRT and the recovery of skilled forelimb function facilitated by FLU. Notably, the blockade of CRT demonstrated that the administration of FLU during the early phase, from one day after ICH (D1) to D5, is crucial for recovery. To assess the qualitative restoration of forelimb function, we performed a kinematic analysis of the recovered forelimb function: each reaching movement was recorded using five synchronized high-speed cameras, and positional data were estimated via DeepLabCut, and three-dimensional information was reconstructed using DiPP Motion V. In addition to a significant increase in the pellet retrieval success rate by FLU, the finger shape significantly differed between the ICH and FLU-ICH groups. A positive correlation between the mean finger distance and the success rate was observed in the FLU-ICH group. The trajectory of each finger was impaired by ICH; however, this impairment was ameliorated in the FLU-ICH group. Interestingly, CRT blockade with clozapine N-oxide significantly reduced success rates, but the positive correlation remained. The blockade also resulted in a greater deviation of the trajectory, indicating ataxia. These data indicate that kinematic changes occur due to switching of neural circuits in the motor control system as well as the motor descending system.

Disclosures: S. Tominaga: None. **S. Ueno:** None. **M. Shindo:** None. **N. Tajiri:** None. **K. Kobayashi:** None. **H. Hida:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.17/DD7

Topic: F.02. Cerebellum

Support: UM1MH130981
Allen Institute

Title: Targeted enrichment of rare cell populations enables comprehensive transcriptomic mapping of the adult human and macaque cerebellum

Authors: A. D. GARCIA[1], W. HO[1], C. M. SOBIESKI[1], R. FERRER[1], D. YUAN[1], J. MAHONEY[1], D. HU[2], F. YAZDANIBANAFSHEDARAGH[2], S. BARTA[1], T. CASPER[1], A. CHAKKA[1], N. DEE[1], J. GOLDY[1], N. JOHANSEN[1], D. L. JONES[1], B. P. LEVI[1], N. PENA[1], N. SHAPOVALOVA[1], A. TORKELSON[1], J. ARIZA TORRES[1], L. KRUSE[1], K. SMITH[1], C. D. KEENE[3], W. FREIWALD[2], T. BAKKEN[1], H. ZENG[1], E. LEIN[1], ***R. D. HODGE**[1];
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Abstract: The cerebellum is integral for a multitude of complex motor and cognitive functions, and lesions to this region produce deficits in motor coordination, spatial cognition, language, and working memory. Despite the functional importance of this structure, the transcriptomic cell types comprising the primate cerebellum remain poorly characterized relative to rodent models. A critical challenge in cerebellar transcriptomics is the severe underrepresentation of functionally important but numerically sparse cell types. To address this challenge, we developed and applied targeted antibody labeling and flow cytometric-based enrichment strategies to specifically boost coverage of Purkinje cells (PCs) and unipolar brush cells (UBCs), two rare populations routinely underrepresented in standard single nucleus transcriptomic datasets. We combined rare cell type enrichments with extensive 10X Next-GEM Multiome sampling across the major axes of the human and macaque cerebellum as part of Brain Initiative Cell Atlas Network (BICAN) efforts to create a comprehensive cross-species taxonomy of the primate brain. Integration of these enrichment datasets with our broad cerebellar sampling revealed a previously unreported complexity of both UBCs and PCs that appears conserved across humans and macaques. Preliminary comparison of differential gene expression and label transfer from published datasets demonstrated the presence of all previously reported cerebellar types in both species including granule neurons, deep cerebellar nuclei excitatory neurons, Golgi neurons, and molecular layer interneurons (MLIs). MLIs resolved into two major classes: NXPH+ neurons that have been proposed to directly inhibit PCs and SORCS3+/PTPRK+ neurons that target other MLIs, resulting in disinhibition of PCs. Each of these MLI classes further resolve into multiple subtypes, providing evidence for heterogeneous populations beyond these two broad distinctions. Taken together, the enrichment strategies developed here were essential for achieving a comprehensive transcriptomic map of the primate cerebellum and similar strategies should prove broadly useful for profiling rare neuronal populations in other brain regions.

Disclosures: A.D. Garcia: None. **W. Ho:** None. **C.M. Sobieski:** None. **R. Ferrer:** None. **D. Yuan:** None. **J. Mahoney:** None. **D. Hu:** None. **F. YazdaniBanafsheDaragh:** None. **S. Barta:** None. **T. Casper:** None. **A. Chakka:** None. **N. Dee:** None. **J. Goldy:** None. **N. Johansen:**

None. **D.L. Jones:** None. **B.P. Levi:** None. **N. Pena:** None. **N. Shapovalova:** None. **A. Torkelson:** None. **J. Ariza Torres:** None. **L. Kruse:** None. **K. Smith:** None. **C.D. Keene:** None. **W. Freiwald:** None. **T. Bakken:** None. **H. Zeng:** None. **E. Lein:** None. **R.D. Hodge:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.18/DD8

Topic: F.02. Cerebellum

Support: R01 NS123933
R01 NS134868

Title: Loss of dystrophin reduces CB1 receptor expression and endocannabinoid-dependent synaptic plasticity in the cerebellar cortex

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Abstract: Duchenne Muscular Dystrophy (DMD) is a debilitating degenerative condition with complex musculoskeletal and cognitive symptoms. The protein responsible, dystrophin, is expressed in both muscle tissue and within the central nervous system (CNS) where it localizes to a subset of inhibitory synapses, including those found on Purkinje cells of the cerebellum. Our previous work focused on loss of inhibitory synapse number and strength in dystrophin-deficient mice, but did not examine other synaptic signaling systems. Recent work has shown that dystrophin loss in skeletal muscle leads to abnormalities in endocannabinoid signaling, particularly related to Cannabinoid Receptor Type 1 (CB1R) signaling pathways. CB1Rs are highly expressed throughout the CNS and have been implicated in short- and long-term plasticity mechanisms. Despite this curious overlap, no work examines how dystrophin loss impacts CB1R signaling in the CNS, a mechanism that may contribute to the diverse neurological pathologies seen in DMD patients. To address this, we used a combination of immunofluorescent labeling and ex vivo electrophysiology to examine CB1R signaling at three classes of synapses within the cerebellum. Utilizing DMD^{mdx} mice, a mouse model of DMD, we find that loss of dystrophin significantly impairs CB1R signaling specifically at parallel fiber-Purkinje Cell synapses, a key location for cerebellar learning. We also find that endocannabinoid-mediated short-term depression is significantly reduced at these synapses, while long-term depression (LTD) is absent. We hypothesize that loss of inhibition in DMD^{mdx} mice results in excessive LTD, down-regulation of CB1Rs and saturation of LTD mechanisms at parallel fiber synapses. To test this hypothesis, we administered diazepam, a positive allosteric modulator of $GABA_A$ receptors, over a 24 hr period in vivo. We find that diazepam recovers endocannabinoid-mediated short-term depression to magnitudes observed in WT littermates. These data suggest that loss of

endocannabinoid signaling and synaptic plasticity may contribute to cerebellar dysfunction and motor control symptoms in DMD. Further, diazepam administration may be a potential therapeutic to restore inhibition and recover endocannabinoid-mediated plasticity in the cerebellar circuit in DMD.

Disclosures: E. Averyt: None. **S. Mitra:** None. **J.R. Pugh:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.19/DD9

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

Support: CIHR PJT180635

Title: Delineating the regulation of cerebellar Purkinje cell excitability and synaptic connectivity by the gamma protocadherins

Authors: *J. H. LI[1], J. MAROCHA[2,3], L.-Y. WANG[2,4], J. L. LEFEBVRE[2,3];
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Abstract: The clustered protocadherins (cPcdhs) are a large family of cell adhesion molecules widely expressed across the brain. They consist of over 50 isoforms in the α-, β, and γ-Pcdh subfamilies. Each isoform has specific homophilic binding, making the combinatorial expression of cPcdh isoforms a substrate for specific cell-surface interactions. These features are what allow cPcdhs to control multiple aspects of neuronal and glial morphological development. Additionally, emerging evidence suggests cPcdhs also regulate synaptic connectivity. However, how they might affect neuronal function (e.g., by affecting synaptic transmission, or neuronal excitability) remains unclear. To address this gap, we are studying cerebellar Purkinje cells (PCs) in mice with PC-specific gamma-protocadherin (γ-Pcdh) deletion. We have previously shown that γ-Pcdhs are required for the development of PC dendritic morphology. Furthermore, mutant mice exhibit defects in motor coordination and motor learning. To understand how loss of γ-Pcdhs results in these functional deficits, we first considered the field-favoured hypothesis that γ-Pcdhs regulate synaptic connectivity. Immunolabeling of synapses onto PCs revealed that the density and size of parallel fibre terminals (VGluT1+) and inhibitory synapses (gephyrin+) were intact in γ-Pcdh cKO mice. In contrast, we observed altered distribution of climbing fibre terminals (VGluT2+) in mutant pups (postnatal day (P)10) but not adults (P30), suggesting developmental progression may be perturbed. Overall, we find no gross effects of γ-Pcdh deletion on synaptic connectivity. On the other hand, patch-clamp recordings revealed a surprising effect on intrinsic (synapse-independent) firing. γ-Pcdh cKO PCs display depressed firing and reduced spiking in response to current injections, a measure of intrinsic excitability.

This may result from an upregulation of K+ current in mutant PCs, apparently from the K+ channel Kv3.3. Kv3.3 are voltage-gated K+ channels which enable high frequency firing, and are widely expressed in fast-spiking neuronal populations (including PCs). Using a CHO cell line expressing Kv3.3 channels, we show that co-expressing γ-Pcdhs inhibits Kv3.3 currents. Ongoing work aims to uncover the molecular mechanism of interaction between γ-Pcdhs and Kv3.3. In summary, we find a novel role of the γ-Pcdhs in regulating intrinsic neuronal excitability, by regulating voltage-gated potassium channels. We propose that these ubiquitous molecules shape circuit function both through their canonical roles in morphological/synaptic development, and by directly tuning intrinsic electrophysiological properties.

Disclosures: J.H. Li: None. **J. Marocha:** None. **L. Wang:** None. **J.L. Lefebvre:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.20/DD10

Topic: F.02. Cerebellum

Support: NIH grant OD030496
NIH grant OD026560

Title: Sex difference in rat cerebellar vermal Purkinje cell size due to both gonadal sex and sex chromosomes

Authors: S. ROBINSON[1], E. POPESCU[1], I. WRIGHT[2], X. CHEN[3], A. M. GEURTS[4], A. P. ARNOLD[5], ***W. E. GRISHAM**[2];
[1]Psychology, [3]Integrative Biol. and Physiol., [2]UCLA, Los Angeles, CA; [4]Physiol., Med. Col. of Wisconsin, Milwaukee, WI; [5]Dept Integrative Biol. and Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Sex differences due to both sex chromosomes (XY > XX) or gonads (Testes > Ovaries) have been detected in cerebellar vermis with MRI scans of a Four Core Genotypes (FCG) mouse model (Corre et al., 2014). Here we 1) expand research on the cerebellar vermis in a rat FCG model, 2) look for cellular size differences attributable to gonadal sex and/or sex chromosomes and 3) describe Purkinje cells (PC) size across lobules. Rats were from the Four Core Genotypes model (Arnold et al., 2026). We compared the mean areas of PC in the cerebellar vermis in XY gonadal male rats (XYT, N=11), gonadal female rats (XXO N=9), XY rats with a disrupted Sry gene and ovaries (XYO, N=8), XX rats with testes due to the insertion of the Sry gene into Chr11 (XXT, N=6), and XY gonadal male rats with an Sry transgene on Chr11 (XYTG, N=5). Cerebella were cut at 40µm in the sagittal plane and stained with thionin. Two to six photographs at 50x were taken per lobule in the cerebellar vermis, and photos ranged across each vermal lobule. Cell areas (µm) were measured manually using FIJI software. PC areas were averaged within each lobule for each animal. XYT & XYTG were combined due to

no difference between means. An ANOVA with 2 between factors with 2 levels each (gonad O vs. T, and chromosomes XX vs.XY) and 1 within factor (lobule) with 9 levels was run. There was an effect for gonad on PC size, O > T $F(1,34) = 8.269$, $p = 0.007$, $\eta 2 = 0.065$, an effect for chromosome, XX > XY, $F(1,34) = 4.174$, $p = 0.049$, $\eta 2 = 0.033$, and a PC size difference across lobules $F(9,306) = 4.745$, $p < 0.001$, $\eta 2 = 0.073$. In a further analysis, four levels of group (XYT, XXO, XYO, XXT) were a between subjects variable and lobule was a within. This analysis revealed a significant difference among groups, $F(3,34) = 5.477$, $p = 0.004$, $\eta 2 = 0.126$. Posthoc Holm tests showed XXO > XYT, $p = 0.002$, and a trend toward a gonadal difference within the XX genotype, XXO > XXT ($p = 0.072$). Our results were consistent with Corre et al.'s vermis volume finding for chromosomes (XX > XY) as well as Lerch et al. (2026) which found an O > T difference, particularly in the caudal cerebellum. Our data may shed light on cellular differences underlying sex differences in cerebellar volumes.

Disclosures: S. Robinson: None. **E. Popescu:** None. **I. Wright:** None. **X. Chen:** None. **A.M. Geurts:** None. **A.P. Arnold:** None. **W.E. Grisham:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.21/DD11

Topic: F.02. Cerebellum

Support: NIH Grant 5R01AG069970-03
NIH Grant P20GM144230.
NIH Grant P20GM121322

Title: The Distribution of Estrogen Receptors in the Adult Rabbit Cerebellar Cortex

Authors: *D. TALKINGTON[1], E. IREWOLE[2], B. G. SCHREURS[2];
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Abstract: The cerebellum contributes to motor coordination and timing and is increasingly recognized for its roles in learning and broader cognitive and affective processes. Steroid hormones, including estradiol, influence cerebellar development and adult physiology. For example, rodent studies have shown that estradiol can modulate cerebellar synaptic transmission, including neurotransmission at the parallel fiber-Purkinje cell synapse. Despite estrogen's clear importance in cerebellar circuits, the anatomical distribution of estrogen receptor subtypes within the adult cerebellar cortex is not well characterized. Here, we mapped the distribution of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) in adult female rabbit cerebellar cortex using immunofluorescence, confocal imaging, and quantitative image analysis (n = 8 rabbits). ERα immunoreactivity was significantly higher in the molecular layer than in the granule cell layer ($p = 0.005$). In contrast, ERβ fluorescence intensity did not differ significantly across the molecular layer, granule cell layer, and white matter ($p = 0.069$). Within the molecular layer,

ERα occupied a significantly greater area fraction than ERβ ($p = 0.002$), suggesting broader spatial occupancy of ERα signal within molecular layer structures. Exploratory comparisons between gonadectomized and sham-operated rabbits did not show significant differences in receptor distribution ($p>0.05$), although this is still being investigated. Together, these findings demonstrate distinct spatial distributions of ERα and ERβ in adult rabbit cerebellar cortex and provide a foundation for future studies linking estrogen receptor localization to cerebellar circuit function.

Disclosures: D. Talkington: None. **E. Irewole:** None. **B.G. Schreurs:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.22/DD12

Topic: F.02. Cerebellum

Support: NIH NS109077-06A1

Title: Calcium Signaling and Behavioral Effects of SCA1 in PFC and DCN

Authors: *E. LABRADA[1], M. CVETANOVIC[2];
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Abstract: Spinocerebellar Ataxia type 1 (SCA1) is a neurodegenerative disease characterized by progressive motor impairment and severe degeneration of cerebellar cells. Calcium signaling plays a crucial role in the brain by regulating various cellular processes. Calcium ions (Ca^{2+}) act as secondary messengers, influencing neurotransmitter release, synaptic plasticity, gene expression, and neuronal excitability. We explored functional changes in the Prefrontal Cortex (PFC) and the Deep Cerebellar Nuclei (DCN) during early- and late-stage disease progression using a knock-in mouse model and fiber photometry to record neuronal calcium activity in healthy and SCA1-affected mice during behavioral and motor tests. We observed changes in calcium activity across different behaviors, primarily in the area under the curve rather than in amplitude, indicating shifts in calcium dynamics and event duration.

Disclosures: E. Labrada: None. **M. Cvetanovic:** None.

Poster

PSTR232: Cerebellum: Cells, Circuits, and Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR232.23/DD13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01NS133694

Title: Bub1b deletion in excitatory cerebellar neurons compromises progenitor expansion and cerebellar growth

Authors: ***A. S. LEE**[1], J. DAM[2], K. RAJAVONG[2], B. K. TERRY[2], A. M. RAJADHYAKSHA[1], S. H. KIM[2];
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Abstract: Budding Uninhibited by Benzimidazole 1B (*BUB1B*) is a mosaic variegated aneuploidy (MVA)-associated gene that encodes BUBR1, a core member of the spindle assembly checkpoint complex that ensures proper kinetochore-spindle attachment and chromosome segregation. In addition to microcephaly of the cerebral cortex, patients with *BUB1B* mutations can also exhibit Dandy-Walker malformations, a congenital brain malformation characterized by incomplete formation of the cerebellar vermis. Loss of *Bub1b* in mice results in massive cell death and reduced cortical cell number during neurogenesis, but the role of *Bub1b* in developing cerebellar granule cell progenitors (GCPs), as well as the underlying molecular and cellular mechanisms, remains unknown. Furthermore, although GCPs are highly mitotic during postnatal development, the role of spindle assembly checkpoint components in GCP expansion and cerebellar growth is not well understood. In this study, we generated mice with conditional deletion of *Bub1b* in the excitatory cerebellar lineage using *Atoh1-Cre* and observed cerebellar hypoplasia starting at embryonic day 18 that persisted through postnatal day 21 (P21). At P0, *Bub1b*-deficient mice exhibited a significant reduction in the number of PAX6+ GCPs and M-phase GCPs, marked by phospho-histone H3 (PH3), in the external granule cell layer. This reduction was accompanied by a significant increase in apoptotic GCPs, marked by cleaved caspase-3, and GCPs with DNA double-strand breaks, marked by γH2AX. To test whether DNA damage leads to p53 activation and apoptosis of GCPs, we co-deleted *Trp53* in *Bub1b*-deficient mice. We observed a partial rescue of PAX6+ GCP number and M-phase GCPs; however, apoptosis and DNA double-strand breaks persisted at P0, suggesting a possible P53-independent apoptotic mechanism. Interestingly, cerebellar vermis hypoplasia was partially rescued at P0, but not at P7 or P21. Together, this study identifies a potential pathogenic mechanism underlying cerebellar hypoplasia in patients with MVA and reveals an essential role for a core spindle assembly checkpoint component in GCP survival, mitosis, and cerebellar growth.

Disclosures: A.S. Lee: None. **J. Dam:** None. **K. Rajavong:** None. **B.K. Terry:** None. **A.M. Rajadhyaksha:** None. **S.H. Kim:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.01/DD14

Topic: F.04. Voluntary Movements

Support: JSPS Grant 23K16631
JSPS Grant 26K20924

Title: Sequential representation of force-related signals across cortical and cervical spinal circuits in humans

Authors: *N. USUDA[1], S. K. SUGAWARA[2], S. LIN[3], H. FUKUYAMA[4], K. AMEMIYA[4], Y. NISHIMURA[3];
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Abstract: In non-human primates, neuronal activity is observed not only in the cerebral cortex but also in the cervical spinal cord before and during voluntary movements. While cortical activity is known to represent specific movement parameters such as direction, timing, and force, it remains unclear what motor information is encoded by spinal activity. In particular, it is unknown whether preparatory spinal activity reflects upcoming movement timing or force output. Using simultaneous brain-spinal cord fMRI, we examined neural activity across cortical and cervical spinal regions and determined their trial-by-trial relationships with reaction time (RT) and peak grip force (PF) during the preparation and execution phases of a hand-squeeze task in healthy volunteers.Twenty-four healthy participants underwent simultaneous brain-spinal cord fMRI using a 3T MRI scanner, while performing a Ready-Set-Go task. We measured PF and RT on a trial-by-trial basis. At the cortical level, the limited sensorimotor region was activated during preparation, whereas widespread higher-order sensorimotor regions were engaged during execution. At the spinal cord level, task-related activity during execution was restricted to the cervical enlargement, which innervates hand muscles, whereas no significant activation was observed during preparation. Despite the absence of significant preparatory spinal activation, trial-by-trial variations in PF were significantly associated with activity in the C3 spinal segment as well as the sensorimotor region during preparation. During execution, PF was strongly associated with activity in cortical sensorimotor regions and the C7 spinal cord. In contrast, RT-related activity was observed in cortical regions during preparation but not in the cervical spinal cord, indicating that spinal activity preferentially reflects force-related rather than timing-related aspects of upcoming movement. Moreover, C7 ventral horn activity during execution mediated the association between preparatory activity in the C3 segment and trial-by-trial PF, suggesting a functional role of upper cervical circuits in relaying force-related motor commands to lower cervical motor circuits.These results reveal a hierarchical representation of force-related signals across the corticospinal axis. Force-related information emerges in cortical motor areas and the upper cervical cord during movement preparation and subsequently in lower cervical motor nuclei during execution, supporting a role for upper cervical circuits, including the propriospinal system, in the transmission of force-related motor commands.

Disclosures: N. Usuda: None. **S.K. Sugawara:** None. **S. Lin:** None. **H. Fukuyama:** None. **K. Amemiya:** None. **Y. Nishimura:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.02/DD15

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number 22K11654
JSPS KAKENHI Grant Number 25K14766

Title: Direction-dependent effects of gravity on speed-accuracy trade-off during vertical pointing movements

Authors: *S. OKUUCHI, K. KUSHIRO;
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Abstract: Human body movements exhibit an intrinsic trade-off between speed and accuracy. Fitts (1954) originally demonstrated that the movement time (MT) can be predicted by movement distance (A) and target size (W): $MT = a + b \times \log_2(2A/W)$, where a and b represent the intercept and slope, respectively. Although this model has been extended and modified for two-dimensional horizontal movements, its application to three-dimensional movements requires consideration of the effect of gravity acting along the vertical axis, which remains unclear. To address this, we investigated how gravity affects the temporal properties for vertical pointing movements. Participants (N = 12) performed upper limb movements toward targets of varying directions, sizes, and distances as quickly and accurately as possible. The obtained MTs were fitted using Fitts's equation, and the slope parameter b, reflecting the sensitivity of MT to changes in movement distance and target size, was calculated and compared between movement directions. The results showed that MTs were longer for downward movements than those for upward movements. In addition, the slope factor b was larger for downward movements than that for upward movements, indicating that MT for downward movements increased more with changes in movement distance and target size. Furthermore, the time required for acceleration and deceleration exhibited direction-dependent differences. These results suggest that gravity asymmetrically affects the speed-accuracy trade-off of upper limb movements depending on movement direction.

Disclosures: S. Okuuchi: None. **K. Kushiro:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.03/DD16

Topic: F.04. Voluntary Movements

Title: Effective connectivity in large scale networks in obsessive compulsive disorder: Aberrant directional network interactions revealed by regression DCM

Authors: *M. RUJAN[1], J. HADOUS[1], V. A. DIWADKAR[2], D. R. ROSENBERG[4], J. A. STANLEY[3];
[1]Wayne State Univ., Detroit, MI; [2]Psychiatry & Behavioral Neurosci., [3]Psych & Behav Neurosci, Wayne State Univ. SOM, Detroit, MI; [4]Dept Psychiatry, Wayne State Sch. Med., Detroit, MI

Abstract: Obsessive Compulsive Disorder (OCD) is characterized by uncontrollable thoughts (obsessions) that lead to compulsive behaviors. OCD is associated with cross-cerebral network dysfunction in task-active and task-free states. Effective connectivity (EC) analyses using dynamic causal modeling (DCM) have revealed *systemic* dysfunction in directional network interactions (Yacou et al., 2022). However, classical DCM is restricted to *small-scale networks* (~6-8 brain regions). Here, we used regression DCM (Frassle et al., 2017) to estimate differences in *large scale* EC across a connectome derived from an initial set of 246 cerebral regions (Fan et al., 2016). fMRI data (n=86 participants, OCD=37, HC=49) were collected using a visuo-motor response task where we manipulated the certainty of the stimulus - response relationship across two conditions (Meram et al., 2021). From the time series, we estimated a full functional connectivity (FC, zero-lag bivariate correlation) matrix ($^{246}C_2$=30,135 cells) for each condition/participant. Statistically significant effects (FC ≠ 0) were identified in each group, before deriving an overlapping significance set (HC ∩ OCD), with quantification of the frequency with which each of the 246 regions contributed to significant effects. The lower 50% percentile of regions in each lobe were pruned (for computational tractability), leaving a still large network of 123 cerebral regions. From the time series, we estimated EC parameters. T-tests were performed between the two groups on the derived parameters ($p<0.05$). Next, we partitioned the significance map (|EC|OCD > |EC|HC; |EC|HC > |EC|OCD), following which we quantified regional source and target frequencies (i.e., how frequently was a region a source/target in a pathway with significant EC) for each of the 123 regions in each partition (HC, OCD). Finally, we quantified inter-group differences (HC ≠ OCD) in source-target frequencies. These differences revealed compelling increases in source-ness and target-ness in OCD. Increased source-ness was found for regions in the bilateral thalamus (sensory gating)(Sherman & Guillery, 2002), the inferior temporal cortex (action)(Federico et al., 2023) and the left anterior and mid-cingulate cortices (cognitive & motor control)(Paus, 2001). In parallel, increased target-ness was seen for regions in the inferior frontal gyrus (response inhibition)(Picton et al., 2007), the pre-central gyrus (motor execution)(Morris et al., 2018), the insula (inhibitory control)(Eggert et al., 2025) and visual cortex. These results reveal the complexity of EC alterations in OCD, and their relation to task-evoked information in fMRI signals.

Disclosures: M. Rujan: None. **J. Hadous:** None. **V.A. Diwadkar:** None. **D.R. Rosenberg:** None. **J.A. Stanley:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.04/DD17

Topic: F.04. Voluntary Movements

Title: Multi-finger synergies and their reflections in synergic adjustments of referent coordinates during force/moment production tasks

Authors: M. KHAN[1], *M. L. LATASH[2];
[1]Kinesiology, Pennsylvania State Univ., University Park, PA; [2]Kinesiology, Penn State Univ., University Park, PA

Abstract: We tested two theories of motor control: control with spatial referent coordinates (RCs) for the effectors, and synergic control of movement stability. In particular, we focused on the relations of force/moment stabilizing synergies during multi-finger tasks in the space of finger forces and in the spaces of linear and rotational RCs. Fourteen young healthy participants performed accurate force/moment combinations in isometric conditions. The "inverse piano" device was used to lift the fingers by different magnitudes (from 0.5 to 2.0 cm over 0.5 s) in such a way that the hand, as a whole, was lifted and rotated into pronation or supination by about 9°. The instruction was not to react to hand motion voluntarily. Linear regressions of force vs. coordinate and moment vs. hand orientation angle were used to estimate RCs and hand referent orientation (RO) as well as linear and rotational apparent stiffness (k), which were interpreted as mechanical reflections of two basic commands, reciprocal and coactivation. Randomization analysis and hyperbolic regression were used to estimate synergies in the {RC; k} spaces stabilizing total force and total moment. The uncontrolled manifold (UCM) toolbox was used to estimate synergies in the space of finger forces over the steady state just prior to the "inverse piano" action. Very strong synergies in the finger force space stabilized both total force and moment, with the synergy index $\Delta V \approx 1.25$ in all conditions and variance within the UCM more than an order of magnitude larger than orthogonal to it. In contrast, synergies in the {RC; k} space were weaker, present at the group level but less consistent across subjects, particularly in pronation tasks, in contrast to earlier studies of accurate force production. These findings could result from interactions of rotational and linear task components, which make linear approximations of the {RC; k} variables less reliable.

Disclosures: M. Khan: None. **M.L. Latash:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.05/DD18

Topic: F.04. Voluntary Movements

Support: NIH R00NS124748
NIH DP2NS142717
Brain Research Foundation Seed

Title: A novel closed-loop tactile interface for investigating sensorimotor integration

Authors: B. SCARLETT[1], V. SINHA[2], *P. KHANNA[2];
[1]Neurosci., [2]UC Berkeley, Berkeley, CA

Abstract: To move successfully, we must sense our bodies and environment. This is evident when participants attempt to strike a match to light a candle after fingertip tactile feedback is numbed. Despite intact vision and motor pathways participants clumsily fumble and fail. While the importance of sensorimotor integration (SMI) is clear, how the brain actively processes afferent somatosensory signals to enable excellent movement control remains unclear.A major challenge in studying SMI precisely is that peripheral somatosensory signals are difficult to measure, especially during movement. Furthermore, because these signals are highly correlated with movement control signals, it is difficult to determine whether monitored neural activity in sensorimotor brain regions represents somatosensory inputs, motor commands, or a combination of both. To address this, we developed a novel experimental paradigm where a gentle, spatially specific airjet stream applied to the stationary palmar surface of one hand is controlled in real-time. Control is driven either by a joystick held in the other hand (human study) or by a brain-machine interface (BMI) driven by chronically monitored motor cortex neurons (animal study). Because the sensing limb is stationary, time-varying proprioceptive signals are minimized, and the delivered tactile feedback is fully characterized.In humans, this reduced system enables behavioral studies of how control changes with sensory acuity, how much of the motor response to unexpected errors stems from proprioception versus tactile processing, and how active versus passive touch compare during object classification. We evaluate sensory acuity by comparing airjet cursor control across skin regions with different tactile receptor densities. To isolate tactile error responses, we introduce sudden cursor jumps during control trials and measure correction latency. Finally, to study active versus passive touch, we encode virtual object outlines in the task. During the active condition participants manipulate the airjet cursor with their joystick to identify shapes. During the passive condition participants experience airjet trajectories replayed from prior trials.With animal subjects performing motor cortex-driven BMI control alongside simultaneous recordings from somatosensory cortex, we can precisely study how these regions communicate during a task with clear separation between motor commands and well-characterized sensory feedback. Ultimately, this paradigm provides a powerful framework to untangle how primates process and actively integrate tactile feedback to guide dexterous motor control.

Disclosures: B. Scarlett: None. **V. Sinha:** None. **P. Khanna:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.06/DD19

Topic: F.04. Voluntary Movements

Title: Precise measure of abnormal grasping force during isometric strength and reaching assessment in chronic stroke-related hemiparesis.

Authors: J. GYARMATY, A. ACOSTA, A. MANDANA, R. FOREMAN, E. HAMILTON, Z. R. PEACOCK, C. WARMBIER, A. WU, O. YOUNG, ***M. D. ELLIS**;
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Abstract: Flexion synergy is a common motor impairment following stroke characterized by abnormal coupling of shoulder, elbow, and wrist flexor muscles, which limits independent joint control and functional upper extremity movement. This abnormal coupling becomes more pronounced as individuals attempt to reach and abduct the arm against an external load compared to when the arm is supported. Methods for the quantification of flexion synergy expression at the shoulder and elbow have been translated to the clinical setting, but limited research has investigated a quantitative method for a global measure of abnormal grasp during arm use suitable for translation. The purpose of this study is to examine differences in abnormal grasp force under different abduction loading conditions during isometric and reaching tasks. We hypothesized that grasp force would be greatest during isometric abduction strength measurement and greater as a function of loading and distance during reaching. Nineteen participants (12 male, 7 female), with chronic stroke (16.40 ± 8.46 years), and mild to severe impairment (Fugl-Meyer score 26.8 ± 13.9) participated in the study. Grasp force was measured using a pressure mat during an individual's maximum isometric shoulder abduction effort and under three loading conditions during reaching manipulated by a mechatronic device currently used in clinical trials. During the reaching conditions, grasp force was measured at a standardized target near the body and at the end of reaching range of motion for each loading condition. We employed two linear mixed effects models using IBM SPSS Statistics: 1. normalized grasp ~ task + (1|*subject*) and 2. normalized grasp ~ task x target + (1|*subject*). The first model yielded a main effect of loading task (isometrics and reaching) ($F(1077.81) = 347.49$, $p < 0.001$) with maximum isometric abduction producing the greatest abnormal grasp ($\beta = 0.508$, SE = 0.017, $t(29.606) = 4.263$, $p<0.001$, 95% CI [0.475, 0.542]). The second model yielded main effects of task ($F(894.91) = 31.40$, $p < 0.001$) and target ($F(891.89) = 295.03$, $p < 0.001$) and an interaction effect ($F(891.89) = 4.42$, $p < 0.001$) with reaching to end range producing greater abnormal grasp ($\beta = 0.103$, SE =0.014, $t(891.89) = 7.122$, $p < 0.001$, 95% CI [0.075, 0.132]) than at the beginning of the reach. In participants with chronic stroke, abnormal grasp is greatest during isometric abduction strength testing. Furthermore, abnormal grasp is greater at the end of reaching range of motion. These findings support the hypothesis that increased shoulder abduction demand and reaching distance amplify flexion synergy expression at the hand.

Disclosures: J. Gyarmaty: None. **A. Acosta:** None. **A. Mandana:** None. **R. Foreman:** None. **E. Hamilton:** None. **Z.R. Peacock:** None. **C. Warmbier:** None. **A. Wu:** None. **O. Young:** None. **M.D. Ellis:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.07/DD20

Topic: F.04. Voluntary Movements

Support: VA Grant 1IK2RX005319-01A1

Title: Quantifying Discomfort and Sensorimotor Recruitment During Transcutaneous Spinal Cord Stimulation

Authors: *J. ESSEMIAH[1,2], L. ABRERA[1], B. THAPA[1], P. GIBSON[3], J. MKRTICHYAN[3], J. S. CALVERT[1];
[1]Dept. of Neurolog. Surgery, [2]Ctr. for Neurosci., [3]Univ. of California, Davis, Davis, CA

Abstract: Transcutaneous spinal cord stimulation (tSCS) has emerged as a noninvasive research technique capable of engaging sensorimotor circuitry and facilitating motor output in individuals with spinal cord injury (SCI). Although tSCS has translational potential as a neuromodulation tool, the discomfort induced by tSCS remains the largest barrier to clinical translation, and there is a lack of understanding on the sensory consequences of tSCS in humans. This study aimed to characterize the motor and sensory effects of tSCS to determine the relationship between stimulation intensity, motor recruitment, and perceived discomfort as well as characterize the sensory percepts evoked by stimulation. Ten neurologically intact participants received tSCS starting at 5mA and increasing to the participant's maximum tolerated amplitude. These stimulations were produced with two different modalities: paired pulse stimulation and continuous stimulation (30 Hz) across five different locations along the spinal cord. The center electrode was placed intervertebrally between T12 and L1, while the other four electrodes were positioned at cardinal points around the center electrode. Two electrodes were positioned on the rostrocaudal axis at adjacent intervertebral levels and two were positioned laterally 2 cm from the center electrode. Motor responses were quantified using bilateral surface electromyography (EMG) recordings from five lower-extremity muscles. Sensory percepts were directly reported through a tablet interface and discomfort was assessed using visual analog scale ratings. We found that continuous stimulation induced discomfort at significantly lower stimulation amplitudes and that the location of stimulation was correlated with both sensory and motor recruitment. These findings provide guidance for selecting stimulation parameters that maximize motor recruitment while minimizing discomfort, a critical step toward the broader clinical implementation of tSCS.

Disclosures: J. Essemiah: None. **L. Abrera:** None. **B. Thapa:** None. **P. Gibson:** None. **J. Mkrtichyan:** None. **J.S. Calvert:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.08/DD21

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI Grant Number JP24K02788

Title: Success-based exploratory learning enhances short-term retention of non-dominant arm choice

Authors: *S. UEHARA[1], K. TAN[2], S. TANABE[1];
[2]Dept. of Rehabil. Med., [1]Fujita Hlth. Univ., Toyoake / Aichi, Japan

Abstract: The use of the affected upper limb in daily activities is challenging for individuals after stroke, limiting the amount of use and the potential for motor recovery. Binary feedback regarding behavioral success or failure is known to regulate motor actions; successful outcomes are reinforced, while unfavorable outcomes are avoided through exploration. Here, in young healthy volunteers, we investigated the effect of success-based exploratory learning on the choice of the non-dominant arm in a reaching behavior and its subsequent short-term retention. In Experiment 1, healthy right-handed volunteers (n = 15) repeatedly performed a forced-choice reaching task in which they reached toward a visual target, displayed at one of the nine locations distributed horizontally and uniformly on the computer screen, with either arm as quickly as possible. Binary feedback of success or failure was provided after each trial based on the arm used. The probability of success feedback was manipulated: 80% when the non-dominant (left) side was used and 20% when the dominant (right) side was used. To evaluate the training effect, we calculated the probability of selecting the non-dominant arm for each target without providing binary feedback, and estimated the point of subjective equality (PSE), the location where either arm was equally likely to be used. The results showed that the probability of non-dominant arm use gradually increased with feedback prioritizing its choice. This tendency remained even without feedback, shifting the PSE toward the right side of the reaching space. However, similar immediate shifts were observed in another control group (n = 15) who simply experienced a gradual increase in non-dominant arm use in a forced manner without success-related feedback. In Experiment 2, we tested the potential difference in the short-term retention of this acquired behavior. Newly recruited participants (n = 15) replicated the gradual increase in non-dominant arm use through manipulated success feedback as in Experiment 1, and further demonstrated significantly better subsequent retention of the reinforced behavior immediately and 60 minutes after training compared to a control group (n = 15) who experienced the forced increase in arm use. These results indicate that arm preference can be effectively modulated from

the dominant to the non-dominant side through success-based exploratory learning. Our findings provide practical insights into the significance of success-feedback-driven exploration for altering habitual motor behaviors in clinical populations.

Disclosures: S. Uehara: None. **K. Tan:** None. **S. Tanabe:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.09/DD22

Topic: F.04. Voluntary Movements

Title: Delta phase resetting in the ventrointermediate thalamus may facilitate coupling to motor cortex

Authors: *G. PAIER[1], E. BENCE[2], E. L. LEVIN[4], K. CHEN[4], D. K. LEVENTHAL[3], E. OPRI[2];
[2]BME, [3]Neurol., [1]Univ. of Michigan, Ann Arbor, MI; [4]Neurosurg., Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Individuals with severe and medically refractory Essential Tremor (ET) can be effectively treated with deep brain stimulation (DBS). Standard DBS treatment entails continuous high-frequency stimulation of the ventrointermediate thalamus (VIM). This treatment, however, ignores underlying neurophysiological and motor behavior. By understanding changes in VIM behavior with respect to movement, the spatiotemporal efficacy of DBS can be improved. Motor cortical β activity (13-30Hz) is transient with movement (Jasper & Penfield 1949), but what internal dynamics influence this behavior must be further investigated. In humans, Saleh et al. 2010 showed that intraregional δ (0.5-4Hz) phase modulation of cortical β amplitude encodes motor task attentiveness before movement initiation. Opri et al. 2019 demonstrated thalamic influence on cortical excitability, with VIM β phase significantly coupling to cortical γ amplitude during movement. The influence of low frequency (8-20Hz) VIM activity on cortical β activity was investigated in Steina et al. 2025. They showed a significant increase in coherence between these signals at the start of movement, but did not consider VIM δ activity. Gaidica et al. 2020 found motor thalamus δ modulates β and γ motor signals within rat motor thalami, exhibiting its importance in motor control. We hypothesized that movement-related δ phase resetting in the VIM organizes thalamic excitability to coordinate β-band activity in the motor cortex. Using the cued-movement dataset from Opri et al. 2019, we found a significant increase in VIM δ phase coupling to cortical β amplitude during the cue-to-movement period for contralateral movements ($p<0.05$ compared to a surrogate dataset). We found that this phase amplitude coupling (PAC) peaks at the start of movement with an average increase of 78.2% from rest. To further investigate this behavior, we collected intraoperative VIM local field potentials from 6 ET patients undergoing DBS surgery. In this task, patients

were visually cued to reach a randomly placed target on a touchscreen with the hand contralateral to the DBS implant. We found a significant phase preference ($p<0.001$ from the K-S test for nonuniformity) towards the π phase of δ at the start of movement, with a pairwise phase consistency (PPC) of 0.62 ($p<0.001$ compared to a surrogate dataset). These results suggest that movement-related δ phase may organize transient thalamic network states to coordinate VIM-motor cortex communication, further recapitulated by the PAC. Future phase-timed stimulation experiments will test whether targeting this state can causally modulate motor circuit dynamics and motor-relevant behavior.

Disclosures: G. Paier: None. **E. Bence:** None. **E.L. Levin:** None. **K. Chen:** None. **D.K. Leventhal:** None. **E. Opri:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.10/DD23

Topic: F.04. Voluntary Movements

Support: Seed Funding Hertie Foundation (Network for Excellence in Clinical Neuroscience)

Title: Intrinsic timescales in the human subthalamic nucleus and their relevance for motor function

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Abstract: Intrinsic neural timescales reflect the capacity of neural circuits to structure and maintain neural activity over time. In the neocortex, they are considered a fundamental organizational principle of the cortical hierarchy underlying higher cognitive functions. Much less is known about intrinsic timescales of subcortical regions, which are characterized by a distinct cytoarchitecture. Recordings from deep brain stimulation electrodes implanted in the subthalamic nucleus (STN) of patients with Parkinson's disease provide a unique opportunity to study this open question, but pathological beta-band oscillations may mask true intrinsic timescales. Here, we estimated intrinsic timescales from the autocorrelation structure of STN local field potentials, both in the unmedicated state and following levodopa administration, while explicitly controlling for the impact of neuronal oscillations. Longer timescales were associated with better motor performance, specifically in the ipsilateral STN during volitional movements.

Critically, these effects were independent of changes in aperiodic activity and oscillatory dynamics, including beta-band power. Together, our findings provide direct evidence that intrinsic timescales are a behaviorally relevant property of the human STN, thus extending their functional significance from the neocortex into subcortical motor circuits.

Disclosures: L. Heidiri: None. **A.A. Kuehn:** None. **W. Neumann:** None. **R.F. Helfrich:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.11/DD24

Topic: F.04. Voluntary Movements

Support: NIH DP2NS142717

Title: Behavioral signatures of prediction in contact events during movement execution and learning

Authors: *H. ZHUANG[1], J. LEE[2], S. CHAUDHARY[4], W. KIM[5], T. OPPENHEIM[3], P. KHANNA[6];
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Abstract: Unseen object interactions rely heavily on somatosensory contact events such as feeling thefingers touch the object, sensing object lift-off, and detecting object contact with a surface.These events indicate that the next movement phase can start. While these events are essentialfor even well-practiced object interactions, what the characteristics are of contact events as amovement sequence evolves from completely unpredicted to well-practiced and fully predictableis unclear. One possibility is that contact events become less informative as action sequencesbecome predictable and are therefore gated by the somatosensory system. Alternatively,contact events may remain informative, with predictability enabling more efficient detection andexecution.We present a novel object manipulation apparatus where participants grip an object that isconstrained to move in a 2D plane while walls are actuated in the 3rd dimension to block orpermit movement of the object respectively. The wall configuration is unseen to participants,forcing them to rely only on contact events to navigate. In the first experiment, participantsperformed a sequence of two movements where they experienced a contact event with ahorizontal or vertical wall after the first movement. In predictable trials, both wall orientation andmovement direction were cued; in direction-predictable/contact-unpredictable trials, onlymovement direction was cued; and in unpredictable trials, neither was cued, requiringparticipants to infer movement direction from wall orientation. In the second sequence learningexperiment, participants navigated to a starting position in the 2D plane and were

instructed tofind a path through the plane to a final target location.We find that contact events in unpredictable trials from the first experiment were associated withreduced approach speed, altered grip force dynamics, and distinct movement kinematicscompared to predictable trials. These behavioral features distinguish between: unpredictablecontact events which are used to gather information about an unknown environment, andpredicted contact events which are only necessary to detect so as trigger subsequentmovement. Using these features, we trained a classifier that locates individual contact eventsalong the spectrum from “predictable” to “unpredictable”. We then use the classifier projection toshow a transition from unpredictable to over sequence learning from the second experiment.Overall, we have identified the behavioral signatures of prediction in contact events, and relatethe transition from events becoming predictable to improvements in motor sequence learning.

Disclosures: H. Zhuang: None. **J. Lee:** None. **S. Chaudhary:** None. **W. Kim:** None. **T. Oppenheim:** None. **P. Khanna:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.12/DD25

Topic: F.04. Voluntary Movements

Support: NSF BCS2444305

Title: Somatosensory realignment following adaptation alters motor planning

Authors: R. MARBAKER, A. L. WONG, *A. S. THERRIEN;
Jefferson Moss Rehabil. Res. Inst., Thomas Jefferson Univ., Elkins Park, PA

Abstract: Estimates of the current body state are critical for accurate motor planning. Body state estimation is thought to rely on both peripheral sensory feedback and predictive information derived from motor commands, and growing evidence suggests that the relative reliance on these signals depends on whether the brain is estimating stationary body position or ongoing movement. While the former relies more on integrating peripheral feedback across sensory modalities, the latter may depend more on predictive signals. We recently demonstrated this dissociation using a force-field perturbation. Following adaptation to the force field, perception of arm movement realigned in the direction of the perturbation, whereas perception of static arm position remained unchanged. Here, we asked whether this perceptual dissociation has separable consequences on subsequent motor planning.Thirty-four neurotypical individuals adapted their reaching movements to counter a velocity-dependent clockwise (CW) or counterclockwise (CCW) curl field. Sensory realignment was determined using reports of static position or movement path following passive displacement of the arm. To probe subsequent effects on motor planning, we compared corrections to two types of mid-reach target shifts. In jump trials,

the target shifted during the reach, requiring online corrections planned according to the current hand position that was estimated while moving. In pause trials, the reach was briefly stopped before the target shift, so corrections were planned from a static hand position. We hypothesized that selective realignment of movement perception toward the direction of the force perturbation would bias state estimates only during movements, exacerbating reach errors when making corrections on jump trials but not on pause trials. Results showed mixed sensory realignment following adaptation. Neither the CW nor the CCW group showed realignment of arm position perception, while only the CCW group showed significant realignment of arm movement perception. Subject-level analysis showed a significant interaction between the movement-perception realignment and the difference in reach errors between jump and pause trials, such that greater realignment of arm movement perception was associated with greater reach errors in the expected direction on jump compared to pause trials. These results align with prior literature and suggest that differences in state estimation between static and dynamic contexts exert dissociable effects on motor planning.

Disclosures: R. Marbaker: None. **A.L. Wong:** None. **A.S. Therrien:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.13/DD26

Topic: F.04. Voluntary Movements

Support: NIH DP2NS142717
NIH R00NS124748
Alfred P. Sloan

Title: A paradigm to study how the predictability of contact events shape planning and execution in sequential movements.

Authors: *W. KIM[1], P. KHANNA[2];
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Abstract: Sequential movements we do every day such as reaching to, grasping, and transporting an object are often segmented by somatosensory “contact events” that mark the end of one submovement and cue the initiation of the next (Flanagan, 2006). When reaching without vision—e.g., into a backpack to find a vibrating phone—the timing of a contact event may be unpredictable, and if expected contact is never detected, the subsequent submovement must be cancelled. How does the brain prepare and execute submovements under uncertainty and possible cancellation? These questions are well studied for reaching movements initiated from rest, but not for ongoing movements. Predictably-timed “go cues” yield faster reaction times than unpredictably-timed ones, and preparation occurs just before a predictable cue but well before an

unpredictable one. The possibility of withholding a response slows reaction time. We ask whether these predictability and cancellation eZects hold when planning and executing a second movement triggered by a self-generated contact event—evidence that the brain re-uses its rest-initiation machinery during ongoing movement. Human participants held a Kinarm manipulandum with their right arm. A haptic vibration at the start position (fast vs slow) instructed the direction of an upcoming second movement (upward or downward), so its direction was known in advance. Participants moved laterally to contact a virtual haptic wall, which cued the pre-instructed second movement. Varying the start-to-wall distance was used to set the contact event's predictability: its location was shown beforehand in expected-timing (ET) but not in unexpected-timing (UT) trials. An additional condition included catch trials with no wall (ET-C) which required second movement cancellation. We extracted second-movement onset and co-articulation before contact. Preliminary observations suggest that ET trials show greater co-articulation (curvature during the first movement) and earlier second-movement initiation than UT trials, with eZects much smaller when comparing ET-C to UT. Altogether, these results suggest that much like in planning from stationary positions, planning while moving is flexible, occurring early or late relative to the cue, and both the predictability of the contact event and the possibility of cancellation influence how much pre-planning occurs. Future work will pair this in macaques with Neuropixels recordings in motor cortex, motor thalamus, and somatosensory cortex to study how contact event predictability updates planning and execution of secondary movements.

Disclosures: W. Kim: None. **P. Khanna:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.14/DD27

Topic: F.04. Voluntary Movements

Title: Neuromechanical responses to changing loading demands assessed using high-density electromyography and ultrasound imaging

Authors: *Z. WANG;
Kinesiology, Washington State Univ., Pullman, WA

Abstract: The nervous system continuously regulates muscle activation to accommodate changing mechanical demands. However, how neural control signals interact with internal mechanical states under varying external loads remains poorly understood. Understanding this interaction is fundamental to elucidating the principles governing neuromechanical regulation in biological movement systems. The present study investigates neural and mechanical responses to changing loading demands using a multimodal framework integrating high-density electromyography (HD-EMG), force measurement, and ultrasound imaging.Healthy adults

performed isometric force-production tasks under multiple loading conditions and load-transition paradigms. HD-EMG was used to characterize the magnitude and spatial organization of muscle activation, while ultrasound imaging was used to assess internal mechanical features during steady-state loading. Force output was simultaneously monitored to quantify external mechanical demand. Neural activation metrics and ultrasound-derived measures were compared across loading levels and transition conditions to examine how the neuromuscular system accommodates changing task requirements.Preliminary observations indicate that neural activation magnitude scales systematically with increasing load, whereas the spatial organization of activation remains relatively stable during steady-state contractions. Ongoing analyses are evaluating whether changes in loading demand and load-transition dynamics are associated with distinct neural activation strategies and corresponding alterations in internal mechanical state.These findings establish a multimodal framework for investigating the interaction between neural control and internal mechanics across varying loading conditions. This work provides an initial step toward understanding the principles by which biological systems regulate internal mechanical states in response to changing external demands.

Disclosures: Z. Wang: None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.15/DD28

Topic: F.04. Voluntary Movements

Title: Personalized Spinal Cord Ultrasound Stimulation Enhances Motor and Somatosensory Pathway Excitability in Humans

Authors: *L. HOU, Y. LEI;
Texas A&M Univ., College Station, TX

Abstract: Low-intensity focused ultrasound (LIFU) is a promising, non-invasive neuromodulation technology with the potential to target spinal neural activity. This study investigated whether a personalized spinal cord ultrasound stimulation (SCUS) approach—which optimizes focal depth based on individual spinal anatomy—can effectively modulate corticospinal and somatosensory pathway excitability. Across two experiments, we targeted the T1 spinal level using a 500 kHz four-element annular array transducer, calibrated to subject-specific spinal dimensions. The SCUS paradigm consisted of 500-ms pulse trains (1000 Hz, 30% duty cycle) delivered every 2 s for 8 min at a free-field spatial-peak pulse-average intensity (Isppa) of 15 W/cm^2. In Experiment 1, we assessed motor excitability by recording transcranial magnetic stimulation (TMS)-elicited motor-evoked potentials (MEPs) from the first dorsal interosseous (FDI; primarily T1-innervated) and extensor digitorum communis (EDC; primarily C7-innervated) muscles before and up to 40 min after active or sham SCUS. In Experiment 2, we

evaluated somatosensory excitability by recording median nerve-elicited somatosensory-evoked potentials (SEPs) via electroencephalogram (EEG) under the same active and sham conditions. Results from Experiment 1 demonstrated that active SCUS produced sustained, selective increases in FDI MEP amplitudes at 5, 20, and 40 min post-stimulation, leaving EDC responses unchanged. In Experiment 2, active SCUS significantly enhanced the early N20/P25 SEP component, but not the later P25/N33 component. In contrast, neither experiment revealed any significant pre-to-post changes in the sham groups. These findings demonstrate that accounting for individual anatomical variation through personalized ultrasound targeting enhances the specificity and efficacy of spinal neuromodulation. This non-invasive, pathway-specific approach holds significant promise for individualized neurorehabilitation.

Disclosures: L. Hou: None. **Y. Lei:** None.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.16/DD29

Topic: F.04. Voluntary Movements

Support: NINDS Grant U01NS132788

Title: Distinct human single-neuron representation of stopping and switching action in subthalamic nucleus

Authors: *D. SUBRAMANIAN[1], J. CHOI[1], S. ZHONG[2], M. YEBRA[3], T. K. NGUYEN[1], Z. FU[1], A. MAMELAK[3], J. R. WESSEL[4], U. RUTISHAUSER[3], V. N. CHRISTOPOULOS[2], N. POURATIAN[1];
[1]UT Southwestern Med. Ctr., Dallas, TX; [2]USC, Los Angeles, CA; [3]Cedars-Sinai Med. Ctr., Los Angeles, CA; [4]The Univ. of Iowa, Iowa City, IA

Abstract: Humans dynamically regulate ongoing actions by stopping or switching behavior in response to changing environmental demands. While both functions are critical, the precise behavioral and electrophysiological relationship between stopping and switching in humans remains incompletely understood. We aimed to delineate the neural mechanisms underlying these core action-regulation functions by studying whether the firing patterns of the subthalamic nucleus (STN) neurons are the same or different for stopping/switching behaviors. We recruited thirteen patients with Parkinson's disease (PD) undergoing deep brain stimulation implantation surgery targeting the STN. Participants performed tasks requiring intermittent stopping or switching directions (up or down) while rapidly moving a joystick horizontally (left or right) in response to visual cues. During the task, we intraoperatively recorded single-neuron activity from the STN and across patients, we recorded 122 neurons. Neuronal responses were evaluated using cluster-based permutation testing, a non-parametric statistical method to identify time

periods in which firing rates following the cue significantly differed from pre-cue baseline. We identified stop- or switch-responsive cells showing task-related changes in firing rates following the respective cues. Neurons were classified as "stop-signal responsive" if firing rate following the onset of a stop-signal was significantly different from the pre-stop baseline. Similarly, switch-signal and movement-responsive neurons were identified based on switch cue- or movement-related changes in firing activity. Approximately 7% of the STN neurons (9 of 122) were responsive to the stop signal while only 1% (1 of 122) were responsive to the switch signal. These stop or switch signal responsive neurons responded only to stop or switch signals respectively but not to movement. Notably, no neuron responded to both stop and switch signals. 25% of the STN neurons (31 of 122) showed movement-related modulation. Some STN neurons (3%, 4 of 122) encoded movement along with stop/switch information. These findings suggest that stopping and switching actions are represented differently in the human STN at the single neuron level. The low prevalence of switch-responsive neurons, together with the absence of neurons jointly encoding both stop and switch signals, suggests that STN microcircuits may be preferentially involved in stopping actions rather than broadly mediating all forms of action regulation.

Disclosures: D. Subramanian: None. **J. Choi:** None. **S. Zhong:** None. **M. Yebra:** None. **T.K. Nguyen:** None. **Z. Fu:** None. **A. Mamelak:** None. **J.R. Wessel:** None. **U. Rutishauser:** None. **V.N. Christopoulos:** None. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Abbott, Boston Scientific, Medtronic, BrainLab.

Poster

PSTR233: Action/Sensation/Movement Selection: Human (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR233.17/DD30

Topic: F.04. Voluntary Movements

Support: NIH Grant U01NS132788

Title: Shared and distinct mechanisms of stopping and switching actions in human cortico-subthalamic circuits

Authors: *J. CHOI[1], D. SUBRAMANIAN[1], S. ZHONG[2], M. YEBRA[3], J. R. WESSEL[4], U. RUTISHAUSER[3], V. N. CHRISTOPOULOS[2], N. POURATIAN[1];
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Abstract: Dynamic action regulation, including the ability to stop or switch ongoing actions, is essential for flexible behavior. However, the behavioral and electrophysiological relationship between stopping and switching remains incompletely understood. Here, we investigated the

neural mechanisms supporting these processes within basal ganglia-cortical motor networks. Thirteen patients with Parkinson's disease undergoing subthalamic nucleus (STN) deep brain stimulation implantation performed joystick-based tasks requiring rapid left/right movements in response to visual cues. In separate blocks, intermittent cues instructed participants either to stop the planned movement or to switch the movement direction (up/down). A simple go task without stop/switch cues served as a control condition. During the task, local field potentials were recorded from the STN, together with cortical signals from primary motor cortex (M1). We compared task-locked oscillatory dynamics across regions and task conditions. Movement onsets were slower during stop-go trials (i.e., go trials in stop task) than simple-go trials, consistent with proactive slowing under stop-signal expectation. Switch-go trials were also slower than simple-go trials but faster than stop-go trials, suggesting an intermediate level of proactive control during action switching. During movement preparation, M1 beta suppression was attenuated in stop-go trials relative to simple-go trials, while switch-go trials showed an intermediate pattern. Go cue-evoked M1 high-gamma activity was also delayed in stop-go trials, indicating delayed recruitment of movement-related cortical activity under stopping demands. During stop trials, successful stopping was associated with delayed M1 beta suppression compared with failed stopping, suggesting that action cancellation partly depended on a less advanced go process before stop-cue presentation. In contrast, pre-switch M1 beta suppression did not differ between successful and failed switch trials. STN beta activity showed similar task-context modulation to M1, but pre-stop STN beta activity did not distinguish successful from failed stopping. These findings suggest that stopping and switching share a proactive motor-control component, reflected by behavioral slowing and attenuated M1/STN beta suppression. However, successful stopping appears to depend more directly on trial-specific M1 motor preparation, whereas switching may rely more on post-cue action reconfiguration than on pre-cue motor suppression.

Disclosures: J. Choi: None. **D. Subramanian:** None. **S. Zhong:** None. **M. Yebra:** None. **J.R. Wessel:** None. **U. Rutishauser:** None. **V.N. Christopoulos:** None. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Abbott, Boston Scientific, Medtronic, and BrainLab.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.01/EE1

Topic: F.04. Voluntary Movements

Support: NSF 2444649

Title: From reaching to intercepting: Target speed shifts the balance between feedforward motor planning and online correction

Authors: *A. MUTTEE[1], R. AMSARAJ[2], J. FRIEDMAN[4], T. SINGH[3];
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Abstract: From squashing a bug to hitting a fastball, humans routinely execute rapid upper limb movements under vastly different task demands. Despite extensive research on reaching and interceptive actions, surprisingly little is known about how motor planning and online correction differ between these two classes of movement. Intercepting a moving target requires predictive, feedforward estimation of future target location and continuous feedback-based correction based on target and hand position, processes that may reshape the motor plan relative to a simple reach. We used submovement (SM) decomposition to quantify how these feedforward and feedback processes are organized within the evolving movement. This approach decomposes hand velocity profiles into overlapping bell-shaped SM, modeling each reach as the summed output of motor primitives defined by onset, duration, and amplitude. By treating the first SM as an index of the feedforward motor plan and later SM as feedback-dependent corrections, we examined both the initial effectiveness of predictive aiming and the corrective structure that unfolds across target speeds. To investigate how these components scale with interception demands, we conducted a two-part study in which Part 1 compared static reaches with moving-target interception, and Part 2 used a more granular range of target speeds. In Part 1, young healthy adults reached to static targets presented at one of two locations or targets originating from those same locations and moving counterclockwise at 75°/s or 150°/s along a circular trajectory. Using a robotic manipulandum, we recorded limb kinematics as well as eye movements and upper-limb EMG. The number of SM were greater for moving targets (75 and 150°/s) than static (0°/s) targets. Additionally, the proportion of trials containing three or four SM increased with target speed, suggesting that faster moving targets required more frequent and vigorous corrective actions. Part 2 extends this analysis using the same paradigm with moving-target speeds of 75, 100, 125, and 150°/s. Preliminary data (n=4) show more SM at 150°/s than at slower speeds and later SM with larger amplitudes as speed increased. After the first SM, angular displacement of the hand-to-target decreased with speed, suggesting that the initial SM was tuned to target speed in a feedforward manner while later SM provided speed-dependent corrective control. Together, these findings suggest that increasing target speed reshapes interception by strengthening predictive feedforward aiming early in the movement while increasing reliance on feedback-based corrections after movement initiation.

Disclosures: A. Muttee: None. **R. Amsaraj:** None. **J. Friedman:** None. **T. Singh:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.02/EE2

Topic: F.04. Voluntary Movements

Support: NSF 2444649

Title: Foveal versus lower-field viewing modulates the magnitude of online reach corrections during standing

Authors: *D. GWON, A. MUTTEE, E. COSTELLA, X. LIU, T. SINGH;
The Pennsylvania State Univ., University Park, PA

Abstract: When a puppy bolts across the floor or a Whack-A-Mole springs up at a new hole, we correct a reach that is already underway — and we do so while standing, worrying about catching the target rather than about staying on our feet. Both how the target changes and where we are looking when it does should matter, and the two examples differ: the puppy moves continuously, whereas the mole jumps to a new spot. This distinction is important — foveal vision, with its high spatial acuity, is suited to localizing a displaced target, whereas the motion sensitivity of peripheral and lower-field vision is suited to registering continuous movement — and may govern how quickly a correction is issued. Standing adds a further demand, since the corrected reach must be supported by the lower-limb postural system. Prior work shows that postural muscle activity precedes corrective arm activity, and, separately, that gaze position relative to a perturbation modulates correction magnitude. How target kinematics and gaze position interact, and how posture is organized around the correction, remains poorly understood. The present study examines this by placing a target that either moves or jumps in either foveal vision (FV) or the lower visual field (LVF). Right-handed individuals performed a fast-paced, forward reach using a KINARM End-Point while standing. During a trial, a target appearing 25 cm from the start position either remained stationary or was displaced 15° (clockwise or counterclockwise) at movement initiation, either gradually (150°/sec) or instantaneously. Gaze was either fixed at the target (FV) or 10 cm (~7° eccentricity) beyond it (LVF). We recorded eye movements, limb kinematics, and EMG data. In preliminary data (n=4), participants showed an anticipatory postural response (bilateral medial gastrocnemius inhibition ~130 ms after target appearance) preceding the reach (reaction time ~350 ms). Online corrections were initiated ~135 ms after visual perturbation; latencies appeared similar across gaze and target conditions. Correction magnitude, measured as lateral hand displacement normalized for speed, was ~21% larger in LVF than FV (4/4 participants). Notably, and in contrast to some previous reports of postural activity leading corrective activity, the corrective response preceded the postural response in all four participants. These preliminary findings suggest that both where a perturbation occurs and how the body is supported shape online corrections, with gaze position modulating correction magnitude and posture potentially following rather than leading the limb during standing.

Disclosures: D. Gwon: None. **A. Muttee:** None. **E. Costella:** None. **X. Liu:** None. **T. Singh:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.03/EE3

Topic: F.04. Voluntary Movements

Support: NSF 2444649

Title: Dissociable Premovement and Post-Movement Beta Dynamics during Interception of Moving Targets

Authors: *J.-H. WU[1], E. COSTELLA[2], X. LIU[1], T. SINGH[3];
[1]Pennsylvania State Univ., State College, PA; [2]Pennsylvania State Univ., Bellefonte, PA;
[3]Kinesiology, Pennsylvania State Univ., University Park, PA

Abstract: Successful interception of moving objects requires integration of visual motion, gaze allocation, motor preparation, and hand execution. Sensorimotor beta-band activity is modulated during movement, but its role during dynamic eye-hand coordination remains unclear. We examined beta desynchronization and behavior during a seated visuomotor interception task. Sixteen healthy adults (7 males, 9 females; age 28.8 ± 4.4 years) performed a Wacom tablet task while 64-channel electroencephalography (EEG), eye tracking, and hand kinematics were recorded. Participants intercepted virtual targets moving leftward or rightward at low, medium, or high speed. Each trial included a 2-s target-preview period followed by an auditory go cue; formal testing included 378 trials per participant across six speed-by-direction conditions. Behavioral analyses showed high overall success (88.1%) and systematic speed-dependent changes: peak velocity increased with target speed and was generally higher for rightward than leftward targets, whereas movement time and reaction time decreased from low to high speed conditions. Gaze and hand trajectories showed the expected sequence: gaze shifted toward the target path during preview, while the hand remained near the start position until after the go cue. EEG analyses focused on beta event-related desynchronization (ERD) during the premovement target-preview period and beta event-related synchronization (ERS)/recovery after the go cue over a C3-centered motor region of interest. Repeated-measures analysis of variance showed no speed effect on premovement beta ERD (low, 2.90 ± 0.15 dB; medium, 2.89 ± 0.14 dB; high, 2.92 ± 0.15 dB, mean ± SEM; p=.907). Rightward targets elicited significantly larger ERD than leftward targets (right, 2.97 ± 0.15 dB; left, 2.83 ± 0.14 dB; p=.042). In contrast, post-go beta ERS/recovery was modulated by speed (low, -3.26 ± 0.18 dB; medium, -3.02 ± 0.15 dB; high, -2.96 ± 0.17 dB; p=.012), with low-speed trials showing more negative beta power than medium (p=.020) and high (p=.021) speeds. Because ERS/post-movement beta synchronization has been linked to sensory feedback processing, movement termination, and speed/acceleration-related movement dynamics, this finding suggests that speed-related beta modulation emerged more clearly after the go cue than during premovement preparation. Thus, target speed modulated task difficulty and movement timing, while premovement beta ERD reflected a general preparatory sensorimotor state, and post-go ERS/recovery reflected speed-sensitive movement execution or feedback-related updating.

Disclosures: J. Wu: None. **E. Costella:** None. **X. Liu:** None. **T. Singh:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

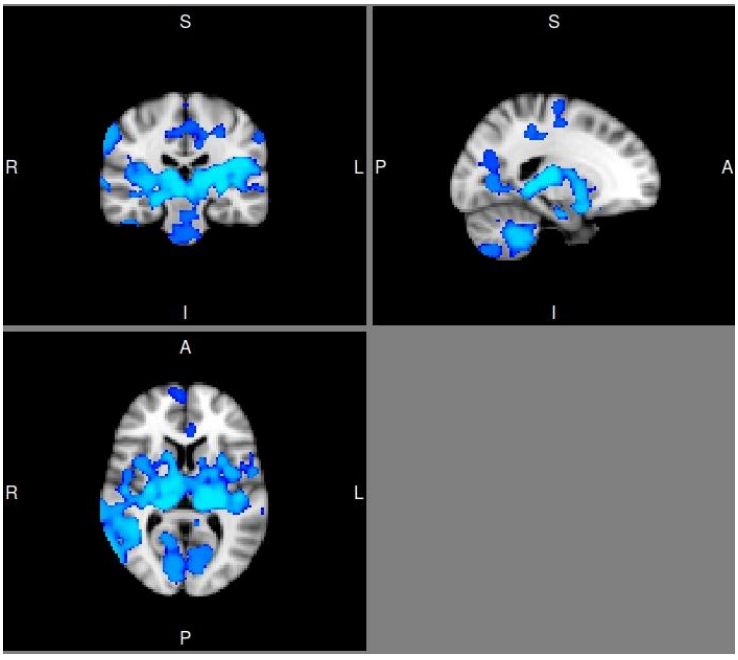
Program #/Poster #: PSTR234.04/EE4

Topic: F.04. Voluntary Movements

Title: DLPFC Functional Connectivity and Fine Motor Performance: A Resting-State fMRI Study

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Abstract: The dorsolateral prefrontal cortex (DLPFC) supports executive control of motor behavior, yet its intrinsic functional connectivity patterns underlying fine motor dexterity remain poorly characterized. We examined the association between bilateral DLPFC resting-state functional connectivity and Grooved Pegboard performance in 373 healthy adults (ages 18-75, 64% female) from the Enhanced Nathan Kline Institute Rockland Sample. Seed to whole brain connectivity maps were generated and whole-brain voxelwise analyses examined connectivity associations with pegboard completion time (dominant hand), controlling for age and sex, using FSL randomise with 5000 permutations and TFCE correction. Slower pegboard performance was significantly associated with reduced DLPFC connectivity to the bilateral cerebellum, thalamus, and posterior parietal cortex ($p < 0.05$, corrected; 44,054 voxels). Peak effects localized to the thalamus (-20, -24, 8) and cerebellar lobule VIIIb (12, -58, -64). No significant Pegboard × Age interaction was observed, indicating that the motor-connectivity relationship was consistent across the adult lifespan. These findings demonstrate that fine motor dexterity is associated with DLPFC connectivity to the cerebello-thalamo-cortical network. Prefrontal-cerebellar functional integration may serve as a neural marker of motor control efficiency in healthy adults.



Disclosures: A. Bishnoi: None. **T. Ikuta:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.05/EE5

Topic: F.04. Voluntary Movements

Support: VCU Breakthroughs Funds

Title: Multimodal Predictors of Resting Motor Threshold and Corticomotor Excitability in Healthy Adults

Authors: *M. PASLAR[1], T. TAYLOR[1], C. LEWIS[2], S. ACHANTA[1], M. FERNANDES GRAGNANI[1], S. SABYASACHI[1], M. S. ALAM[1], W. LOHR[1], J. ATULASIMHA[1], L. MA[1], R. HADIMANI[1], C. L. PETERSON[1];
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Abstract: Background: Resting motor threshold (RMT) and corticomotor excitability vary substantially across healthy adults, limiting the precision of transcranial magnetic stimulation (TMS) dosing and interpretation. Prior studies suggest that both network-level physiology and anatomy contribute to this variability, but most have focused on single modalities. We investigated whether multimodal resting-state features derived from electroencephalography (EEG), functional MRI (fMRI), and diffusion tensor imaging (DTI) can characterize individual differences in RMT and recruitment-curve measures.
Methods: Thirty healthy adults underwent resting-state EEG, MRI/fMRI, and single-pulse TMS over primary motor cortex. EEG sources were reconstructed into 30 regions of interest using linearly constrained minimum variance beamforming. Functional connectivity was quantified using weighted phase lag index and orthogonalized amplitude envelope correlation, including mean, variability, and graph-based metrics. fMRI analyses estimated effective connectivity among motor-relevant resting-state regions. TMS outcomes included RMT and first dorsal interosseous recruitment-curve measures. Correlational tractography was performed with and without coil-to-cortex distance (CCD) as a covariate to assess associations between fractional anisotropy (FA) and RMT.
Results: Source-level EEG processing generated static and dynamic connectivity matrices for all retained regions and yielded subject-level network features across frequency bands. These measures provided both trait-like and time-varying descriptors of motor-network organization. Integration with fMRI effective connectivity and DTI is being used to test whether directed motor-network interactions improve prediction of RMT and recruitment-curve measures beyond EEG features alone.
Conclusions: A multimodal framework combining EEG, fMRI, and DTI is feasible for studying interindividual differences in corticomotor excitability. White matter connectivity showed a

stronger relationship with RMT after accounting for CCD. This approach may help identify biomarkers relevant to personalized TMS dosing and candidate selection for neuromodulation-based rehabilitation.

Disclosures: M. Paslar: None. **T. Taylor:** None. **C. Lewis:** None. **S. Achanta:** None. **M. Fernandes Gragnani:** None. **S. Sabyasachi:** None. **M.S. Alam:** None. **W. Lohr:** None. **J. Atulasimha:** None. **L. Ma:** None. **R. Hadimani:** None. **C.L. Peterson:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.06/EE6

Topic: F.04. Voluntary Movements

Support: NSERC DG RGPIN-2023-05353

Title: Beta-Gamma Coupling Reveals Corticomuscular Communication

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Abstract: *Background: Reliable measures of corticomuscular connectivity are needed to evaluate motor recovery following neurological injury. Corticomuscular coherence (CMC), which quantifies linear coupling between EEG and EMG signals predominantly within the beta band, is the most widely used measure of corticomuscular connectivity. However, significant CMC is detected in roughly 50% of neurologically intact individuals during voluntary contraction, limiting its utility as a biomarker of corticospinal function. Here we systematically examined phase- and amplitude-based relationships between EEG and EMG across beta and gamma frequency bands to gain insight into the neural mechanisms underlying corticomuscular communication.*
Methods: Previously published EEG-EMG recordings from 28 neurologically intact adults were analyzed during sustained plantarflexion contractions and natural standing. EEG was recorded over the sensorimotor cortex and EMG from the soleus muscle. CMC, phase-amplitude coupling (PAC), and phase-locking value (PLV) were quantified within and across beta (15-30 Hz) and gamma (30-150 Hz) frequency bands. Significant PLV relationships were further evaluated using time-lag analysis. Surrogation testing was used to assess if coupling was non-random.
Results: Significant beta-band CMC was detected in 13 of 28 participants (46%) during voluntary contraction and was largely absent during standing. Beta-gamma PAC was observed in a similar proportion of participants as CMC (12/28, 43%), despite characterizing cross-frequency

rather than same-frequency coupling. Beta-gamma PLV demonstrated the highest detection rate (19/28, 68% during seated contraction; 7/28, 25% during standing) and exhibited a peak lag of 38.8 ± 14.4 ms and 38.3 ± 15.0 ms, respectively. Examination of EMG signals further revealed strong beta-band modulation of gamma-band EMG amplitude.
Conclusions: The convergence of CMC, PAC, and PLV findings suggests that these measures reflect different manifestations of a common corticospinal communication process. The combined analysis of CMC, PAC, and PLV leads to the following working hypothesis: burst-like motor cortical activity is not directly observable in scalp EEG, but is reflected in beta-band fluctuations representing the overall activation state of the motor cortical population. These fluctuations modulate the timing and magnitude of gamma-band motor-unit activity, giving rise to CMC, PAC, and PLV as complementary signatures of the same underlying corticospinal mechanism. Under this framework, PAC and PLV may specifically reflect the magnitude and timing of motor-unit population bursts, respectively.

Disclosures: L.P. Zigomanis: None. **H. Kim:** None. **Y. Tian:** None. **M. Zaback:** None. **K. Masani:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.07/EE7

Topic: F.04. Voluntary Movements

Title: Spectral and topographical analysis of EEG rhythms as prognostic insight into the regulation of motor activity and skill acquisition.

Authors: A. POPOV[1], V. GRITSENKO[2], I. ZYMA[3], J. ALVES FERREIRA[4], ***S. TUKAEV**[5]; [1]Electronic Engin. Dept., Igor Sikorsky Kyiv Polytechnic Inst., Kyiv, Ukraine; [2]Human Performance - Physical Therapy, West Virginia Univ., Morgantown, WV; [3]Dept. of Human and Animals Physiol., Taras Shevchenko Natl. Univ. of Kyiv, Inst. of Biol. and Med., Kyiv, Ukraine; [4]Univ. de Coimbra, Coimbra, Portugal; [5]Natl. Taras Shevchenko Univ. of Kyiv, Educational Scientific Inst. of High Technologies, Kyiv, Ukraine

Abstract: Movement is the result of complex brain processes that control limb performance and integrate diverse sensory information. It remains unclear whether distinct neural mechanisms are responsible for the temporal processing of movement initiation and termination. In a study investigating the encoding of temporal information for the initiation and cessation of arm movements using event-related potentials (ERPs), it was found that activity in the premotor area was significantly lower prior to both the initiation and cessation of arm movements in response to time-predictable, as opposed to unpredictable, stimuli. The aim of this study was to delineate the sequence of brain processes involved in movement and to determine the topographical characteristics of movement regulation mechanisms. To identify EEG correlates of voluntary

movement, we analyzed the entire duration of an externally guided motor task, dividing it into several consecutive stages: interstimulus interval, target appearance and movement initiation, execution of movement toward the target, achievement of the target, disappearance of the target as a cue to return, backward movement to the starting position, and movement cessation. EEG analysis enabled the identification of key informational and nodal points in the formation of movement. We hypothesized that differences in EEG activity patterns reflect the specific characteristics of right- versus left-hand movements, with more pronounced adjustment and correction processes for the right hand and weaker ones for the left. In right-handed individuals, right-hand movements are more automated and less reliant on top-down control from the frontal, associative, and sensorimotor cortices. Notably, energy consumption during left-hand movements is likely higher in right-handed subjects.

Disclosures: A. Popov: None. **V. Gritsenko:** None. **I. Zyma:** None. **J. Alves Ferreira:** None. **S. Tukaev:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.08/EE8

Topic: F.04. Voluntary Movements

Title: EEG sample entropy in sensorimotor cortex declines before EMG-defined movement onset.

Authors: *P. J. SCOTT, R. E. HARTMAN;
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Abstract: Electroencephalogram (EEG) entropy is a measure of complexity in cortical activity and may change during motor preparation, but its temporal relationship to movement onset has not been clearly characterized. Chen et al. (2024) found that EEG entropy, EMG entropy, and corticomuscular coupling differ across stages of a grip-and-lift task using the WAY-EEG-GAL dataset from Luciw et al. (2014). The current study used the same dataset to examine whether EEG sample entropy (SampEn) shows a time-locked decline in sensorimotor cortex immediately before EMG-defined movement onset. SampEn was calculated from 2000 ms before to 1998 ms after EMG-defined movement onset during a cued grip-and-lift task in 12 participants (each with 218-274 trials). A sign-flip permutation test showed that sensorimotor SampEn declined significantly during the final ~400 ms before movement onset (p<.001), suggesting reduced cortical complexity during late-stage motor preparation. We also compared SampEn across sensorimotor, frontal, parietal, and occipital regions during the final pre-movement interval, and found that SampEn differed among regions, $F(3, 33)=18.82$, *partial eta-squared*=0.63, Greenhouse-Geisser-corrected p<.001. Bonferroni-corrected pairwise comparisons revealed that sensorimotor SampEn was lower than frontal (d=1.72, p<.001), parietal (d=1.42, p<.001), and

occipital (d=0.74, p<.02) SampEn. Finally, mean SampEn was higher before than after movement onset, Wilcoxon signed-rank test (r=.74, p<.03). Together, these findings suggest that EEG sample entropy decreases in sensorimotor cortex immediately before movement and may index cortical constraint during the transition from motor preparation to movement execution.

Disclosures: P.J. Scott: None. **R.E. Hartman:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.09/Web Only

Topic: F.04. Voluntary Movements

Title: Modulation of muscle hysteresis under conditions of simultaneous changes in force and length of human elbow flexor muscles

Authors: *E. V. KOLOSOVA[1,2], A. V. GORKOVENKO[2], A. I. KOSTYUKOV[2];
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Abstract: Muscle hysteresis, reflecting history-dependent relationship among electromyographic (EMG) activity, muscle length, and force, has traditionally been investigated under fixed-length or fixed-force conditions. However, it remains unclear how hysteresis is affected when muscle length and force change simultaneously. The objective of this study was to determine how combined changes in muscle force and length influence muscle hysteresis in human elbow flexors when their temporal patterns either coincide or oppose one another. Ten healthy right-handed volunteers participated in the study (6 men and 4 women, Mage=26.6, SD=5.4 years). A robotic mechatronic device generated cyclic elbow movements while participants produced voluntary forces guided through visual biofeedback. EMG hysteresis was quantified across different combinations of muscle length and force patterns, both represented by double-trapezoid temporal profiles. Surface EMG signals were recorded using a bioamplifier system (AC-916, CWE, Inc., USA), a CED 1401plus data acquisition unit, and Spike2 software (Cambridge Electronic Design Limited, UK). It was found that the movement-pattern factor with two levels (shortening-lengthening and lengthening-shortening) has statistically significant effect on EMG indices (F=19.962, P=0.002). This finding suggests that EMG parameters of the muscle activity depend, in part, on the muscle length at the onset of movement. The muscle-length-range factor, with two levels (0-0.5 and 0.5-1.0 of maximal muscle length), also significantly affected EMG indices, with higher EMG values observed in the shorter-length range (F=14.206, P<0.001). This effect may reflect both mechanical and neural mechanisms. Changes in joint angle alter muscle length and flexor moment arm, thereby influencing torque production. In addition, suboptimal overlap of actin and myosin filaments at extreme joint positions may reduce contractile efficiency, requiring greater EMG activity to maintain the same load. It was also found that

muscle hysteresis was determined not only by the direction of muscle length change, but also by the direction of the accompanying force change. With increasing the force amplitude in coinciding direction with the length, the amplitude of hysteresis increased, whereas with the same force changes in the opposing direction it decreased markedly and could even become negative, reversing the conventional hysteresis pattern. These findings demonstrate that muscle hysteresis can be significantly dependent on the interaction between changes in muscle force and muscle length, as well as on the preceding movement history.

Disclosures: E.V. Kolosova: None. **A.V. Gorkovenko:** None. **A.I. Kostyukov:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.10/EE9

Topic: F.04. Voluntary Movements

Support: Honda R&D Co., Ltd.
NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc
JST [Moonshot R&D Program] (Grant Number JPMJMS259G-X)
JSPS KAKENHI (Grant Numbers 21H00967 and 26K00595)

Title: Self-generated emotional states shape motor performance through mesolimbic-motor interactions

Authors: *S. LIN[1,2], S. K. SUGAWARA[1], A. SHIINA[3], Y. HOSHI[3], N. USUDA[1], M. NISHIJIMA[3], Y. UEDA[3], J. OKUMA[3], M. MOMOKI[4], T. IBARAKI[4], M. HOSHINO[3], Y. NISHIMURA[1];
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Abstract: Mental imagery in skilled performance often includes anticipated outcomes accompanied by emotional states. Imagining emotional situations modulates motor output, yet the neural mechanisms underlying this effect remain to be clarified. Here, through behavioral and functional MRI studies, we examined whether positive emotional imagery enhances motor performance and identified its neural substrates. In a behavioral study ($N = 39$), participants performed a ready-set-go task under positive, neutral, or no-imagery conditions. Positive imagery increased heart rate and subjective arousal, which were significantly correlated, indicating that heart rate reflects internally generated emotional response. Positive imagery also improved reaction time and peak grip force. Functional MRI study in a separate group of participants ($N = 41$) reproduced the modulatory effect of positive imagery on emotional

response (i.e., increased heart rate) and motor performance (i.e., improved reaction time and peak grip force). Whole-brain analysis revealed that positive imagery increased activity in mesolimbic systems, including the ventral midbrain (VM) and ventral striatum, as well as motor-related areas, including the dorsal and ventral premotor cortices (PMd and PMv) and supplementary motor area (SMA). Imagery-related activity in the VM, ventrolateral thalamus (VL), and putamen predicted subsequent peak grip force, while preparatory activity in the SMA and primary motor cortex (M1) further correlated with both reaction time and peak grip force. Mediation analysis showed that imagery-related activity in PMd, cingulate motor areas, and VL influenced both reaction time and peak force via preparatory M1 activity, whereas imagery-related VM activity influenced peak force only through preparatory M1 activity. These findings indicate that self-generated emotional states act as an internal driver of motor performance, shaping preparatory activity in motor networks through mesolimbic-motor interactions.

Disclosures: S. Lin: None. **S.K. Sugawara:** 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.; NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc.. F. Consulting Fees (e.g., advisory boards); NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc. **A. Shiina:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **Y. Hoshi:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd.. **N. Usuda:** None. **M. Nishijima:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **Y. Ueda:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **J. Okuma:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **M. Momoki:** A. Employment/Salary (full or part-time):; NTT DATA Institute of Management Consulting, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Honda R&D Co.,Ltd. **T. Ibaraki:** A. Employment/Salary (full or part-time):; NTT DATA Institute of Management Consulting, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Honda R&D Co., Ltd. **M. Hoshino:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **Y. Nishimura:** F. Consulting Fees (e.g., advisory boards); NTT DATA INSTITUTE OF MANAGEMENT CONSULTING, Inc..

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.11/EE10

Topic: F.04. Voluntary Movements

Title: TMS-induced Disruption of the Primary Motor Cortex affects Motor Variability but not Motor Output under Visual Feedback

Authors: N. RAO[1,2], ***P. J. PARIKH**[2];
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Abstract: Motor variability affects daily tasks and skill learning. While behavioral and pathological factors affecting motor variability are known, the underlying physiological processes remain unclear. Foundational work suggests that peripheral motor noise cannot account for the majority of force variability. Descending signals from cortical regions such as the primary motor cortex (M1) likely play a crucial role in motor fluctuations during visuomotor tasks. Using grip force production as a model task, the present study aimed to determine the causal role of M1 in regulating motor variability in the presence and absence of visual feedback. Fourteen participants performed an isometric force production task before and after receiving modulatory theta burst stimulation (TBS; a form of repetitive TMS). Participants' neural activity in the M1 was transiently disrupted either using inhibitory cTBS, excitatory iTBS, or sham TMS in separate pseudorandomized sessions at least five days apart. Motor variability was assessed at different force magnitudes (low, medium, high) and with varying visual feedback (present or absent) before and after delivering TMS. With minimal differences in motor variability across pre-TMS conditions, a consistent increase and decrease in motor variability were observed following iTBS (excitatory) and cTBS (inhibitory) when compared to sham stimulation, respectively. This change was dependent on the force magnitude, with elevated variability occurring at medium force levels, whereas reduced variability occurred at higher force levels. This change was observed selectively when visual feedback was present, and not when it was absent. The changes in motor variability occurred without interfering with task performance. The findings establish crucial evidence showing systematic causal contribution from central processes involving M1 to motor variability. Since the TMS-based M1 disruption modulated motor variability without compromising on task performance, the findings argue in favor of the notion that the mechanistic underpinnings of motor variability and motor output are independent and dissociable in nature. The evidence from this study also opens avenues for investigation into broader causal neural substrates underlying motor variability.

Disclosures: N. Rao: None. **P.J. Parikh:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.12/EE11

Topic: F.04. Voluntary Movements

Support: NSF CAREER 1943712
NSF CRCNS 2509333

Title: Dissociating the Neural Control of Force and Impedance Using fMRI and Robotics

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Abstract: Introduction: Humans can interact skillfully with the environment across a wide range of tasks despite uncertainty and disturbances. One mechanism that supports these interactions is the regulation of joint impedance through the simultaneous activation of muscle groups, or muscle coactivation. While there is behavioral evidence for the independent control of coactivation relative to reciprocal activation (Burdet et al. 2001), our understanding of how the brain commands these mechanisms remains limited. In this work, we investigate the neural mechanisms associated with coactivation in a dynamic motor task while controlling for activations related to isolated agonist contractions.
Methods: Thirty healthy, young adults participated in a wrist-pointing functional magnetic resonance imaging study (fMRI) with an fMRI-compatible wrist robot, the MR-SoftWrist (Erwin et al. 2017). Participants were asked to make straight point-to-point movements with their right wrist in flexion-extension, while the MR-SoftWrist applied four types of perturbations in the radial-ulnar deviation direction. These conditions were designed to elicit coactivation (divergent force) while controlling for agonist muscle contraction (constant force up/down) and baseline movement (no force). We modeled neural activity associated with each condition using a general linear model.
To determine whether coactivation relies on distinct neural resources relative to reciprocal activation, we defined three contrasts. First, we tested whether coactivation activity exceeds the linear combination of isolated agonist contractions. Then, we tested whether coactivation responses exceeded either agonist contraction alone. Finally, we used exclusive masking to identify coactivation-related activity in regions showing no response to agonist activation.
Results: All three contrasts identified significant clusters (uncorrected $p<0.001$) primarily in the left premotor, motor, and somatosensory cortices, as well as the right thalamus. The latter two contrasts also showed activation in the right cerebellar lobule V and right inferior parietal lobule. These results suggest coactivation recruits neural resources beyond those required for agonist contractions alone.
Conclusions: We identified physiologically plausible neural correlates of coactivation in a dynamic motor task. Activation in these areas was distinct from reciprocal activation, providing an important step toward more accurate models of human motor control and improved evaluation and treatment of neural injury.

Disclosures: K. Schmidt: None. **F. Sergi:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.13/EE12

Topic: F.04. Voluntary Movements

Title: Motor unit pool activity and time to task failure in healthy young adults

Authors: *T. WORTHINGTON[1], R. J. MALIK[1], W. KIM[1], J. J. KIM[2], V. R. SHANKAR[3], A. M. A. CHAGAS[1], B. YACOUBI KEYHANI[2], E. A. CHRISTOU[4];
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Abstract: Motor unit discharge rates (MUDR) adapt throughout a fatiguing contraction to maintain a constant force output. The purpose of this study was to understand how changes in motor unit pool activity relate to the Time to Task Failure (TTF) of a submaximal isometric contraction. Healthy young adults (N = 8, 3F) performed ankle dorsiflexion and used visual feedback to sustain 25% of their maximum force until task failure. We identified TTF as the duration of the sustained contraction. We recorded high-density surface electromyography from the tibialis anterior (TA) muscle and utilized decomposition software (Delsys Neuromap) to generate individual MUDR signals. To obtain a representation of the motor unit pool activity, we summated the MUDR signals of 5 uniformly selected motor units. We selected the first and last motor unit identified, as well as 3 additional linearly spaced motor units between them based on their order of identification. From the summated MUDR signal, we calculated the mean discharge rate (MDR), standard deviation of the discharge rate (SDDR), and coefficient of variation of the discharge rate (CVDR) for each quarter (Q1, Q2, Q3, Q4) of the participant's sustained contraction. For each of these outcomes, we calculated the absolute difference between adjacent quarters to understand the magnitude of change at different time points in the contraction. MDR significantly differed across the quarters of the contraction ($F(1.5, 10.6) = 20.6$, $p < 0.001$). MDR in Q2 increased from Q1 (Q2 mean = 38.7 Hz; Q1 mean = 34.9 Hz), but pairwise comparisons showed that this difference was not significant ($p = 0.09$). However, we found that the change in MDR from Q1 to Q2 negatively correlated to the TTF ($R2 = 0.67$). The change in MDR between Q2 and Q3 and between Q3 and Q4 did not significantly relate to TTF ($p>0.2$). These findings demonstrate that a greater increase in motor unit pool discharge rate during the first half of a sustained contraction is significantly associated with a shorter TTF. This suggests that early changes in motor unit activity during a sustained contraction may serve as a predictor of impending task failure.

Disclosures: T. Worthington: A. Employment/Salary (full or part-time):; University of Florida. **R.J. Malik:** A. Employment/Salary (full or part-time):; University of Florida. **W. Kim:** None. **J.J. Kim:** A. Employment/Salary (full or part-time):; University of Florida. **V.R. Shankar:** A. Employment/Salary (full or part-time):; University of Florida. **A.M.A. Chagas:** A. Employment/Salary (full or part-time):; University of Florida. **B. Yacoubi Keyhani:** A. Employment/Salary (full or part-time):; University of Florida. **E.A. Christou:** A. Employment/Salary (full or part-time):; University of Florida.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.14/EE13

Topic: F.04. Voluntary Movements

Title: Hidden Features of Performance Fatigability Emerge Across Repeated Fatiguing Trials

Authors: ***R. J. MALIK**[1], V. R. SHANKAR[2], A. M. CHAGAS[1], J. J. KIM[3], T. WORTHINGTON[1], S. KEYHANI[4], E. A. CHRISTOU[5], B. YACOUBI KEYHANI[6]; [1]Univ. of Florida, Gainesville, FL; [2]Applied Physiol. and Kinesiology, Univ. of Florida, Bangalore, India; [3]Applied Physiol. and Kinesiology, Univ. of Florida, Gainesville, FL; [4]Univ. of Florida, Chicago, IL, IL; [5]Applied Physiol. & Kinesiology, [6]Applied Phsio and Kinesiology, Univ. of Florida, Gainesville, FL

Abstract: Performance fatigability reflects the decline in performance during sustained or repeated contractions and is influenced by multiple factors. While previous studies have identified mechanisms such as sex, load, and contraction type as contributors to fatigability, the factors governing performance across repeated fatigue exposures remain unclear. Here, we investigated changes in time to task failure across repeated trials and sought to identify motor and non-motor features associated with performance differences between young male and female adults. Eighteen healthy young adults (22.2 ± 3.9 years, 9 females) completed five consecutive trials of a bilateral upper-limb task to failure separated by 1-min rest. During each trial, participants sustained 90° shoulder flexion while projecting lasers within a 3-cm target displayed on a monitor positioned 2 m away. Time to task failure (TTF) was defined as the time when the arms dropped below a predefined threshold. In addition to TTF, perceived fatigue and pain ratings were obtained after each trial. Baseline force and temporal motor-control performance were quantified using a goal-directed task, while non-motor characteristics were assessed using self-administered questionnaires. Pre- and post-fatigue maximum voluntary contraction (MVC), reaction time, and perceived exertion were also measured. TTF decreased significantly across repeated trials ($p < 0.05$), with a significant sex-by-trial interaction ($p = 0.044$). For Trial 1, males exhibited longer TTF than females (309 s vs. 218 s). However, no sex differences were observed for Trials 2-5. Perceived fatigue and pain ratings did not differ between sexes across trials ($p > 0.05$). Importantly, the mechanisms explaining TTF shifted across repeated fatigue exposures. For Trial 1, TTF was associated with baseline physiological and motor-control features, including shoulder MVC and temporal control measures during the baseline goal directed task ($R^2 = 0.50$, $p < 0.05$). For Trial 3, subjective fatigue severity emerged as the primary predictor of TTF ($R^2 = 0.33$, $p = 0.015$). These initial findings suggest that the mechanisms governing sustained motor performance shift across repeated fatigue exposures. Here, initial performance was primarily influenced by motor features, whereas later performance related with affective factors. Therefore, repeated trails to failure may be valuable to understand the factors driving performance fatigability, especially in neurological disorders where both motor and non-motor systems can be affected.

Disclosures: R.J. Malik: None. **V.R. Shankar:** None. **A.M. Chagas:** None. **J.J. Kim:** None. **T. Worthington:** None. **S. Keyhani:** None. **E.A. Christou:** None. **B. Yacoubi Keyhani:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.15/EE14

Topic: F.04. Voluntary Movements

Support: NIH NCATS Georgia CTSA UL1PR002378

Title: An MRI-compatible touchscreen tablet for continuous tracking of kinematics and force during visuomotor control

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Abstract: Background: Integrating measures of hand kinematics, eye movements, and neural activity offers unique insights into human visuomotor control. Existing MRI-compatible response devices often rely on low sampling rates, discrete responses, or stylus-mediated interactions that do not capture visuomotor processes associated with direct finger contact. We developed an open-source, MRI-compatible touchscreen system optimized for continuous assessment of fingertip position and force during fMRI. Methods: The tablet and stand are constructed from low-cost plastic and non-ferrous materials to minimize RF noise and image artifacts. Custom circuitry supports continuous acquisition of fingertip position and force at 100 Hz. Participants interact with the device using a custom 3D-printed finger attachment that enables direct touchscreen contact without a stylus. Visual stimuli are projected outside the bore and viewed via a mirror. During 3T fMRI (GE Discovery MR750), we synchronously recorded eye position (EyeLink 1000 Plus), fingertip position, fingertip force, and BOLD activity while participants performed visuomotor tracking tasks with varying spatial and temporal demands. Results:The system operated safely at 3T with no detectable reduction in spatial or temporal signal-to-noise ratio. In-scanner use provided reliable, high-frequency measurements of trajectory accuracy, movement variability, online corrective responses, and force modulation, while supporting real-time visual feedback of fingertip position. Across tasks, fMRI data revealed expected activation within frontoparietal, cerebellar, and oculomotor networks associated with coordinated eye-hand control. Conclusions:This accessible MRI-compatible touchscreen platform provides a flexible tool for studying visuomotor behavior by combining high-frequency position tracking, force measurement, direct finger-based interaction, and integrated eye tracking. Its open-source design facilitates replication and customization across scanner environments, enabling mechanistic investigations of human visuomotor function across a wide range of fMRI paradigms.

Disclosures: J. Deitrich: None. **J. McCurdy:** None. **H. Mahmoudi:** None. **E. Courville:** None. **D.A. Barany:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.16/EE15

Topic: F.04. Voluntary Movements

Support: NIH R01NS120226

Title: Reticulospinal-Mediated Shared Neural Drive Across Upper-Limb Muscles During Shoulder Abduction

Authors: *P. SHIH[1], J. P. DEWALD[2], J. YAO[3];
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Abstract: The reticulospinal tract (RST) exhibits branching projections across multiple spinal segments, making it a strong candidate for providing shared neural drive among multiple upper-limb muscles. This anatomical feature allows the central nervous system to use shared drive to support multiple joints simultaneously. However, how this shared drive is organized across flexors and extensors within a distal joint during SABD with increasing load remains unclear. Because startReact-positive (SR+) responses rely primarily on RST-mediated drive, we combined the startReact paradigm with intermuscular coherence (IMC) to noninvasively probe synchronized shared drive in intact humans for the first time.

Twenty-three healthy adults performed SABD at five load levels (25-53% of maximum SABD force). Within each load, trials began with a "Ready" cue (80 dB) followed by either a "Go" (80 dB, n=14) or "Startle" (120 dB, n=6-8) cue 1.5-4.5 s later. Surface electromyography was recorded from the intermedial deltoid and secondary (elbow, wrist, and finger flexors and extensors) muscles. IMC was computed using wavelet coherence on startReact-positive (SR+) trials. Linear mixed-effects models assessed effects of load and muscle group on IMC.

While there was no significant main effect of muscle group ($F(1, 1105.4) = 2.65$, $p = 0.10$), a significant interaction between load and muscle group was observed ($F(1, 2015.6) = 4.11$, $p = 0.043$): a significant negative coherence-load slope was exhibited in extensor muscles ($\beta = -0.0025$, $SE = 0.00080$, $p = 0.0016$), but not in flexor muscles ($\beta = -0.00040$, $SE = 0.00080$, $p = 0.62$).

Our previous work examined RST-mediated flexor/extensor coactivation at the elbow and wrist during SABD across load levels, reporting balanced coactivation between these 2 muscle groups. Consistent with this, the absence of a significant main effect of muscle group on IMC suggests that flexors and extensors receive comparable baseline levels of RST-mediated descending input, supporting joint stability. However, whereas our prior work demonstrated load-dependent

coactivation (an index of shared drive magnitude) in flexors but not extensors, the present findings reveal load-dependent IMC (an index of shared drive synchrony) in extensors but not flexors. Together, these results indicate that the magnitude and synchrony of RST-mediated shared descending input may be regulated through distinct mechanisms across these 2 muscle groups. To our knowledge, this is the first direct evidence of differential RST-mediated control strategies for flexor and extensor muscles, offering a putative neural mechanism for maintaining distal joint control during load-bearing tasks.

Disclosures: P. Shih: None. **J.P. Dewald:** None. **J. Yao:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.17/EE16

Topic: F.04. Voluntary Movements

Support: CTSI-UL1TR002544
NSF-CBET-1804550
NIH-NINDS-R21NS130936

Title: Yank modulates corticospinal output during voluntary submaximal contractions

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Abstract: Impaired grip force termination is a disabling consequence of neurological disorders such as stroke, where sustained finger flexor activity traps objects in the hand. Force generation and release both require a balance of excitation, inhibition, and neuromodulation to scale motor output, yet the neural mechanisms underlying force release remain poorly understood. Motor evoked potentials (MEPs) and motor evoked twitches (METs) are modulated by the rate of force change (yank) during force generation, yet little is known about their characteristics during force release. This study examined METs, antagonist muscle MEPs, and motor unit responses to transcranial magnetic stimulation (TMS) across three force conditions: increase (ramp up), maintenance (static), and release of force (ramp down). After approval by the Northeastern University Institutional Review Board (#15-10-22), 7 healthy participants (3 female; 24.8 ± 7.7 yrs) provided informed written consent following explanation of study procedures. Subjects performed submaximal trapezoidal contractions during index finger abduction. TMS (105% rMT) was delivered over the first dorsal interosseous (FDI) motor cortex representation when participants reached 20% maximal voluntary contraction (MVC) during each condition. METs were extracted from the force signal, MEPs were recorded from the first palmar interosseous (FPI, antagonist) using standard surface EMG electrodes, and FDI motor unit discharges were

decomposed from a 64-channel high-density surface EMG grid. MET amplitude (% MVC) decreased from ramp up (4.3 ± 1.8) to static (2.9 ± 1.5) to ramp down (2.4 ± 0.8). Cortical silent period duration of FDI motor units increased from ramp up to ramp down (ramp up: 137 ± 16.2, static: 143 ± 7.8, ramp down: 171 ± 23.9 ms). The antagonist (FPI) peak-to-peak MEP amplitude (mV) increased from ramp up (1.6 ± 0.8) to static (1.5 ± 0.8) to ramp down (2.4 ± 0.8), despite consistent pre-stimulus background EMG. These findings suggest that force release involves a shift in corticospinal excitability balance, with reduced agonist drive and increased antagonist corticospinal responsiveness in the absence of overt antagonist activation, potentially implicating phase-dependent modulation of reciprocal inhibition in the neural coordination of grip release.

Disclosures: A. Swamy: None. **A. Darendeli:** None. **O. Soto:** None. **E. Tunik:** None. **M. Yarossi:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.18/EE17

Topic: F.04. Voluntary Movements

Support: Natural Sciences and Engineering Research Council of Canada (NSERC): 04899-2023

Title: Influence of vibratory plantar stimulation on cortical motor planning and spatiotemporal step parameters

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Abstract: Walking relies on coordinated neuromuscular control, proactive motor planning, and continuous integration of sensory feedback. The premotor cortex (PMC) supports movement preparation, while plantar mechanoreceptors provide essential input for anticipatory postural adjustments and gait initiation. Although plantar vibratory stimulation has been shown to influence balance and gait variability, its effect on cortical motor planning remains unclear. This study examined whether augmenting plantar mechanoreception with vibratory insoles modulates PMC activity during the planning phase preceding gait initiation and whether PMC activation relates to step width variability (SWV), a measure of lateral stability. In a counterbalanced within-subjects design, thirty-two healthy young adults (18 female; 24 ± 4.4 years) performed single-step initiations in a contingent negative variation-style paradigm. Participants planned and executed either heel-first or toe-first steps under vibration ON and OFF conditions, interspersed with standing rest serving as the baseline control. PMC activity was recorded using functional

near-infrared spectroscopy (fNIRS) and lower-limb kinematics via inertial measurement units. fNIRS data were analyzed using a general linear model, and task-related PMC activation was assessed with repeated-measures ANOVA. Planning a step significantly increased left PMC activation relative to rest ($p=0.007$), indicating cortical engagement during gait initiation planning. However, PMC planning activity did not differ between heel-first and toe-first steps ($p=0.485$), and plantar vibration did not modulate PMC planning activation ($p=0.887$). Left PMC activation was not significantly correlated with SWV. These findings suggest that the PMC is engaged during the planning phase of gait initiation, but acute augmentation of plantar mechanoreception via vibratory insoles does not alter PMC planning activity or predict lateral stepping variability in healthy young adults. Future work should examine whether plantar sensory augmentation influences cortical motor planning under more challenging task demands or in populations with impaired sensory-motor control.

Disclosures: S. Lai: None. **A. Doroodchi:** None. **T. Green:** None. **S. Peters:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.19/EE18

Topic: F.04. Voluntary Movements

Support: PAPIIT DGAPA IN214524

Title: Functional Connectivity of the Action-Observation Network in Patients with Lower Limb Amputations

Authors: *M. CUETO, R. G. PAREDES;
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Abstract: Lower limb amputation induces cerebral neuroplasticity as evaluated by functional magnetic resonance imaging. However, little is known about how network-level functional reorganization of the action-observation network (AON) occurs after lower limb amputations. The AON comprises a broad network of regions, including the posterior superior temporal sulcus (pSTS), the superior parietal lobe (SPL), the inferior parietal lobe (IPL), the ventral premotor cortex (vPM), and the dorsal premotor cortex (dPM). The pSTS is involved in the reasoning of the intentions underlying actions and the perception of biological motion, the SPL plays a role in integrating sensory information and is associated with motor planning functions, the IPL contributes to the formation of a body image and monitors sensory signals representing movements of both the self and others, the vPM and the dPM play an important role in the planning and execution of movements, the first related to objects and the understanding of actions, and the second related with spatial processing and object manipulation. We studied thirty-one unilateral lower limb amputees (AMPs), thirty-two matched healthy controls (HCs),

and thirty-two matched diabetic controls (DCs) using resting-state functional magnetic resonance imaging (rsfMRI). A region of interest (ROI)-wise connectivity analysis was performed with ROIs in fourteen brain regions in the AON to investigate intra-network changes. The ROI-wise connectivity analysis showed that AMPs had increased functional connectivity between the dorsal and ventral premotor cortex ipsilateral to the amputation ($p < 0.05$, FDR corrected). These findings provide insights into cortical reorganization following a lower limb amputation, particularly in regions that play a crucial role in the planning and execution of movements.

Disclosures: M. Cueto: None. **R.G. Paredes:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.20/EE19

Topic: F.04. Voluntary Movements

Support: NINDS Grant R01NS133094

Title: Effects of perturbation and control on scalp map distribution during bimanual coordinative tasks

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Abstract: The cortical network responsible for the sensorimotor control and coordination of bimanual common-goal tasks is not well understood. We used a virtual, bimanual common-goal task that required 11 healthy participants to control the height of a bar with devices that measure grip forces from two hands. Visual perturbations were applied to the bar bilaterally (BP) or unilaterally (UP) and participants were instructed to make the necessary corrections to keep the bar in balance while simultaneously moving the bar to reach the top of the screen. Participants controlled the bar with both hands (BC), the left hand only (LC), or the right hand only (RC). The combination of perturbations and hand control led to 6 experimental conditions within each subject. There were 12 experimental blocks (4 for each control level: BC/LC/RC), and 24 trials per block (random sequence of BP, UP, and no perturbation). Cortical signals were recorded from 64 scalp electroencephalography (EEG) channels. Raw signals were filtered and cleaned via Artifact Subspace Reconstruction (ASR). Independent Component Analysis, dipole fitting, and rejection (with ICLabel) were conducted to further remove artifacts. Kinematic results showed that the time point where participants tend to make corrections after perturbation occur within 200-300ms after perturbation. Topographic ERP analysis with TANOVA showed that there was a significant ($p < 0.05$) effect of Perturbation type on ERP 300ms after perturbation. Additionally, a significant ($p < 0.05$) effect of Control type was found at the same time point. While source-level analysis must still be conducted to identify the location of the differences,

results indicate that there were cortical dynamics in frontal and parietal regions associated with common-goal bimanual coordination. These findings can help further the current body of research into the sensorimotor control of bimanual common-goal tasks and potentially update current rehabilitation methods aimed at regaining upper-limb neuromuscular control post injury/pathology.

Disclosures: R. Francisco: None. **Q. Fu:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.21/EE20

Topic: F.04. Voluntary Movements

Support: Edwin H. Richard and Elisabeth Richard von Matsch Distinguished Professorship in Neurological Diseases (to E.S.-A.)
Shanghai Youth Science and Technology Innovation Plan (22YF1454200 to Y.L.)

Title: Pre-existing Architecture and Compensatory Experiences Predict Functional Reorganization in Individuals Born Without Hands

Authors: *Z. DENG[1], F. A. MARTINEZ-ADDIEGO[1], Y. LIU[2], E. STRIEM-AMIT[1]; [1]Dept. of Neuroscience, Georgetown Univ., Washington, DC; [2]Global Inst. of Future Technology, Shanghai Jiao Tong Univ., Shanghai, China

Abstract: What drives functional reorganization remains a central question in brain plasticity. Individuals born without hands (individuals with upper-limb dysplasia, IDs) provide a unique model: in IDs, the “missing hand” territory in association sensorimotor cortices represents alternative body parts (effectors) with a similar functional role as hands, the feet, which they use for everyday actions. Here, using task-based fMRI response and resting-state connectivity maps, we asked whether foot responses in IDs reflect pre-existing organization existing in typically developed (TDs) individuals, alterations due to compensatory sensorimotor experience, or their combination. We additionally tested whether bottom-up somatotopic or top-down action-level representations better predict this cortical remapping. To test this, we built a voxel-wise multiple linear regression model that uses both pre-existing architectural and experience-dependent connectivity alterations to predict foot selectivity of IDs across the brain. Pre-existing architectural features included typical sensorimotor connectivity patterns (from primary and association sensorimotor cortices) and a higher-level response map, indexing regions where action-type information generalizes across effectors (cross-effector action map) in TDs. Experience-driven connectivity changes included group-difference connectivity maps indexing altered connectivity in IDs relative to TDs from both primary and association motor areas. The model significantly predicted foot selectivity in IDs. When evaluating the specific contribution

of each predictor, the strongest ones were low-level factors: the difference between foot-selective S1/M1 connectivity map and hand-selective S1/M1 connectivity map in TDs, and the experience-dependent alteration of this same contrast between IDs and TDs. In contrast, high-level factors, cross-effector action map, seed-based connectivity maps from the dorsal premotor cortex, as well as another low-level factor, foot S1/M1 connectivity map, did not independently predict functional reorganization in IDs. Together, cortical remapping in congenital handlessness is determined not solely by innate organization but by the interaction between pre-existing architecture and alterations due to compensatory sensorimotor experience. However, top-down modulation seems less predictive of this reorganization than bottom-up somatotopic mapping and its modification. Overall, our findings suggest that functional reorganization arises from experience-dependent remodeling of a pre-existing architecture, primarily driven by bottom-up factors.

Disclosures: Z. Deng: None. **F.A. Martinez-Addiego:** None. **Y. Liu:** None. **E. Striem-Amit:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.22/EE21

Topic: F.04. Voluntary Movements

Support: Philantropic Support

Title: Neurologic Music Therapy and HD-tDCS for Upper Limb Performance in Corticobasal Syndrome: Clinical Outcomes and Preliminary EEG Findings

Authors: *K. KANG[1], I. STERNER[2], A. PANTELYAT[3];
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Abstract: Corticobasal syndrome (CBS) is a progressive neurodegenerative disorder characterized by asymmetric motor impairment, dyspraxia, and functional decline, with limited treatment options. Neurologic Music Therapy (NMT) promotes sensorimotor rehabilitation through structured auditory cueing and therapeutic instrument playing, while high-definition transcranial direct current stimulation (HD-tDCS) may enhance neuroplasticity by modulating cortical excitability. This study examined the clinical and neurophysiological effects of combined NMT and active HD-tDCS and NMT and sham HD-tDCS in CBS. In a triple-masked randomized trial, 20 individuals with CBS received active HD-tDCS+NMT (n=10; 7 females; age 65.5±6.5 years; years since diagnosis 1.49±0.78) or sham HD-tDCS+NMT (n=10; 5 females; age 70.0±4.1 years; years since diagnosis 1.79±0.67) across six 30-minute sessions over three weeks. HD-tDCS targeted sensorimotor regions associated with upper-limb motor planning and

execution. Trial outcomes included the Wolf Motor Function Test (WMFT), Box and Block Test (BBT), Purdue Pegboard Test (PPT) at baseline, post-intervention, and one-month follow-up; resting-state EEG connectivity assessed before and after each treatment session. Significant improvements over time were observed in WMFT, BBT, and PPT for the overall cohort. WMFT demonstrated a significant group×time interaction, with greater improvements in the active HD-tDCS group (T1-T2: $\Delta M=6.30$, $p=0.0002$, $d=1.35$; T1-T3: $\Delta M=7.20$, $p=0.0001$, $d=1.54$), suggesting a possible additive benefit of concurrent HD-tDCS and NMT. Preliminary EEG analyses revealed significant within-group changes in auditory-motor (T8-FC6, T8-C4, T8-CP6) and fronto-motor (FC6-C4) connectivity in the active intervention group, with large between-group effect sizes (Cohen's d =0.90-1.26). Although the statistical significance of these exploratory findings did not survive correction for multiple comparisons, the observed effect sizes suggest potentially meaningful neurophysiological differences associated with active HD-tDCS+NMT. These findings support the feasibility of combining NMT and HD-tDCS in CBS and motivate further investigation of underlying neural mechanisms and efficacy in larger controlled trials.

Disclosures: K. Kang: None. **I. Sterner:** None. **A. Pantelyat:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.23/EE22

Topic: A.07. Development of Neural Systems

Support: Academy of Pediatric Physical Therapy Grant FWA00005078
Department of Defense grant FA9550-24-1-0214
NIGMS 5U54GM104942-08

Title: Beyond Adult Scaling: Growth-Adjusted Musculoskeletal Models for Infant Movement Analysis

Authors: *N. KOLI[1], K. INAMDAR[1], V. GRITSENKO[2];
[2]Human Performance - Physical Therapy, [1]West Virginia Univ., Morgantown, WV

Abstract: Rapid changes in body size, segment proportions, and neuromuscular control accompany infant sensorimotor development. These developmental changes complicate biomechanical modeling because most musculoskeletal models and scaling approaches are derived from adult anthropometry. Adult-based scaling may inaccurately represent infant head, trunk, and limb geometry, affecting estimates of joint centers, segment mass distribution, and dynamic simulations. We developed a growth-adjusted anthropometric scaling framework to generate infant-specific biomechanical models for future OpenSim simulations.Nineteen infants aged 2-6 months were recorded during spontaneous prone movements using three-dimensional

motion capture. Body weight, age, and sex were used with CDC/WHO growth-chart LMS parameters to estimate individual weight-for-age percentiles. Corresponding length-for-age percentiles were then used to estimate body length. An infant-scaled rigid-body model was constructed with physiologically constrained joints and segment geometries represented by ellipsoids, cylinders, and rectangular prisms. Segment lengths were scaled using published infant anthropometric proportions relative to estimated body size. Head diameters and body widths and thicknesses were estimated from proportional relationships in 6-month-old infants. Limb diameters and thicknesses were estimated from proportional relationships in adults. Segment masses were calculated from segment geometry and published tissue densities to derive inertial properties for future simulations.Scaled model dimensions were evaluated by comparing predicted head and shoulder widths with measurements obtained from motion-capture data in infants. The scaled model reproduced characteristic developmental body proportions, including a relatively larger head and trunk proportions in infants compared to adults. Head-height proportion was nearly twice the adult value. Growth-adjusted scaling showed good agreement with motion-capture measurements, yielding mean root-mean-square errors (RMSE) of approximately 3 cm for head and shoulder width. In contrast, adult-based scaling produced errors of up to 6 cm RMSE for head and upper-body dimensions.This framework provides a transparent method for estimating infant-specific segment dimensions and inertial properties from growth-chart data, anthropometric relationships, and motion-capture measurements. The approach may improve quantitative analyses of infant sensorimotor development and support future investigations of both typical and atypical motor development.

Disclosures: N. Koli: None. **K. Inamdar:** None. **V. Gritsenko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurowired.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.24/EE23

Topic: F.04. Voluntary Movements

Support: NSERC Grant
VISTA, Vision: Science to Applications

Title: Neural Mechanisms of Human Eye-Hand Coordination: More Than the Sum of Its Parts

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Abstract: Eye-hand coordination supports many everyday behaviours, yet its neural basis is largely inferred from studies examining saccades and reaches separately. Although overlapping

saccade and reach activity has been proposed to support eye-hand coordination, this hypothesis has rarely been tested directly. Using event-related fMRI, a dedicated eye-hand coordination condition, and a task that separated behaviour into distinct sensorimotor phases, we investigated whether eye-hand coordination simply reflects the sum of eye and hand networks or recruits distinct neural mechanisms.Twenty healthy adults completed a 70-minute fMRI. Using a touchscreen, participants performed 8 functional runs containing randomized saccade, reach, eye-hand coordination, and control trials. Participants encoded a peripheral visual target location, maintained fixation during a 6-s delay, received a cue specifying the effector, completed a second 6-s planning delay, and then executed the movement to the remembered target. Control trials required colour reporting rather than movement. A GLM modelled each action relative to control for each phase. Group-level permutation testing (FWE-corrected, $p<0.05$) identified whole-brain activity. Effector-specific contrasts (EHC>Saccade, EHC>Reach) and their conjunction identified regions preferentially engaged during eye-hand coordination. ROI analyses compared activation magnitude across conditions (rmANOVA, $p<0.05$) beyond overlapping regions.Encoding activated frontal and temporal regions. During planning, saccades recruited limited bilateral occipital and parietal regions, whereas reaches engaged broader occipital, parietal and frontal regions. Eye-hand coordination showed a pattern more closely resembling reaches. During execution, saccade and reach activity involved expected bilateral parietal, frontal, and cerebellar regions, with sensorimotor lateralization for reach. Eye-hand coordination produced more extensive activation than either effector alone. Effector-specific contrasts and conjunction analyses revealed greater eye-hand activity in occipital pole, superior parietal cortex, superior frontal gyrus, supplementary motor area, supramarginal gyrus, and cerebellum. ROI analyses confirmed stronger responses during eye-hand coordination in superior parietal occipital cortex, frontal and supplementary eye fields, and anterior cingulate. Eye-hand coordination cannot be explained by a simple summation of eye and hand networks. Coordinated behaviour recruits additional neural processes, identifying candidate mechanisms underlying human eye-hand coordination.

Disclosures: C. Rubino: None. **K. Masoudi:** None. **J. Crawford:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.25/EE24

Topic: F.04. Voluntary Movements

Support: NIH Grant U01NS117765
Burroughs Wellcome Fund (1379453)
Jane Coffin Childs Memorial Fund for Medical Research (61-1801)
Zuckerman STEM Leadership Program
Rothschild Fellowship

Title: Sensorimotor theta oscillations coordinate speech movements

Authors: *Y. NORMAN[1], L. M. FRANK[2], E. F. CHANG[3];
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Abstract: Fluent speech production requires the brain to generate rapid and tightly coordinated motor commands that orchestrate articulatory movements with millisecond precision across dozens of vocal tract muscles. While previous research has identified distributed neural representations within the ventral sensorimotor cortex (SMC) that encode these movements, a fundamental question remains unanswered: how are these spatially dispersed neuronal populations coordinated in time to generate coherent speech motor output? Using high-density electrocorticography (ECoG), we identified intrinsic 6-10 Hz theta-range oscillations within the SMC that support this coordination. Shortly before speech onset, we observed a significant increase in theta phase coherence among speech-responsive sites spanning the SMC and adjacent cortical regions, forming a distributed theta-coherent speech network. Within this network, high-gamma activity—a proxy for local population firing—was strongly coupled to theta phase, peaking near the trough. Notably, the oscillation maintained stable frequency and amplitude across varying speech rates and cognitive states, consistent with an intrinsically generated rhythm. Control analyses ruled out acoustic feedback and movement-evoked responses as alternative explanations. To investigate the role of this cortical rhythm in articulatory coordination, participants produced hundreds of English sentences while articulatory kinematics were continuously measured using an AI-assisted articulatory inversion approach, enabling tracking of jaw, lip, and tongue movements during speech. Analysis of these kinematic trajectories revealed semi-rhythmic motor events characterized by coordinated, pulse-like changes in articulatory velocity corresponding to constriction gestures associated with phonemes. These pulsatile kinematic changes occurred at an average rate of 7-9 events per second and were strongly coupled to the phase of the sensorimotor oscillation. Mesoscale neural representations associated with these pulses were systematically organized by theta phase, with phoneme identity maximally decodable near the theta trough. Our findings uncover an unrecognized role for theta oscillations in speech motor control, identifying them as an intrinsic temporal scaffold that coordinates motor output across distributed cortical circuits. By synchronizing excitability across spatially dispersed sensorimotor populations, this rhythm may provide a fundamental organizing principle for the rapid and sequential coordination of actions that underlies fluent speech and other complex motor behaviors in the human brain.

Disclosures: Y. Norman: None. **L.M. Frank:** None. **E.F. Chang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Echo Neurotechnologies.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.26/EE25

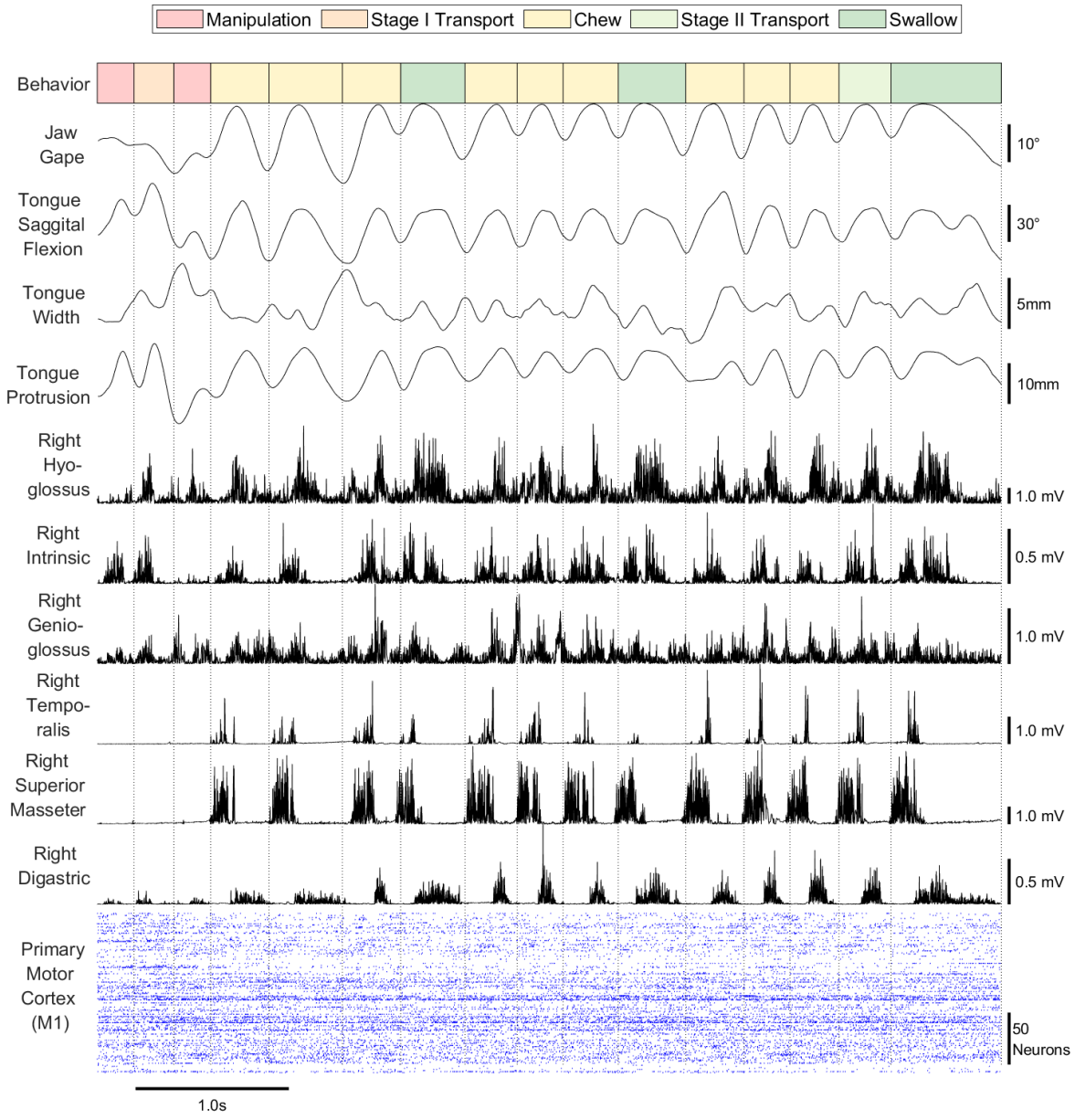
Topic: F.04. Voluntary Movements

Support: 5R01DE027236-06
Ruth L. Kirschstein Interdisciplinary Research Training Award (T90)

Title: Neural Population Dynamics During Feeding

Authors: *D. TANG[1], L. FAVOUR[2], V. HOSACK[2], J.-S. LI[2], S. PUNACHA[2], F. I. ARCE-MCSHANE[2,3];
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Abstract:



Activity in the primary motor cortex (M1) is widely understood to generate voluntary movement in corresponding areas of the body. How essential behaviors such as feeding rely on cortical control of tongue and jaw movements has not been characterized. To investigate the origins of healthy behavior, we used bilateral video radiography and implanted markers to track 3D tongue and jaw movements while male rhesus macaques (n=2) engaged in natural feeding. Simultaneously, we recorded electromyographic signals from muscles of the tongue and jaw and neuronal activity using chronically-implanted microelectrode arrays in M1. We identified five phases of feeding for each cycle of the jaw from max gape to max gape, including chewing and swallowing. A linear discriminant classifier trained on kinematics of tongue and jaw movement and kinetics of tongue and jaw muscle contraction showed high outgroup classification accuracy (65 ± 4%) for the five feeding cycle types. Nearly all (153/154, 31/35) individual M1 neurons exhibited some preferential activation for cycle type, time within each cycle, and chewing sidedness (Kruskal-Wallis test, $p < 0.05$). Principal component analysis revealed low dimensionality (76.0%, 73.9% var explained with first two components) of the population variability during each gape cycle. Gaussian process factor analysis of trials showed distinct rotational dynamics of neural population factors, phase locked to cycles of the jaw. Remarkably, these rotational neural trajectories shifted over the course of the behavior corresponding with the early, middle, and last stages of the feeding. During some stages, subsequent behaviors nearly overlapped, despite being separate, i.e. chewing and swallowing, and dispersion of the neural population trajectory decreased significantly as the trial progressed (Wilcoxon rank sum test, $p < 0.05$). Overall, these results suggest that low dimensional population activity in orofacial M1 exhibit rotations corresponding to the cyclic movements of the tongue and jaw.

Disclosures: D. Tang: None. **L. Favour:** None. **V. Hosack:** None. **J. Li:** None. **S. Punacha:** None. **F.I. Arce-McShane:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.27/EE26

Topic: F.04. Voluntary Movements

Support: University of Washington Mary Gates Research Scholarship
NIA R01AG069227

Title: Inferring functional connectivity of cortical neuron populations with recurrent neural networks and current-based decomposition

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Univ. of Washington, Seattle, WA

Abstract: Brain regions do not operate in isolation but form dynamic circuits whose interactions give rise to coordinated behavior. Disruptions to these circuits underlie neurological disorders such as Alzheimer's and Parkinson's Disease. Classical linear methods for studying neural connectivity fail to capture the nonlinear dynamics that characterize cortical circuits. To address this limitation, this study implements a data-constrained recurrent neural network (RNN) framework, using the chewing cycle as a behavioral model whose rhythmic, repetitive structure allows neural population activity to be precisely aligned and examined at a systems level. We hypothesize that motor and somatosensory cortical regions exhibit asymmetric directional interactions during rhythmic chewing, reflecting a hierarchical circuit organization underlying coordinated orofacial motor behavior.
Neural recordings were collected from a rhesus macaque implanted with microelectrode arrays in rostral motor cortex (rM1), caudal motor cortex (cM1), and somatosensory areas 3a/3b (rS1) and areas 1/2 (cS1). Trial-averaged firing rates from 192 simultaneously recorded neurons across 547 chewing cycles were used to train 20 independent RNNs to reproduce observed population dynamics (best model pVar = 0.784). Current-Based Decomposition (CURBD) was applied to the learned connectivity matrix to extract directed excitatory and inhibitory drive estimates from each source region to each target across the chewing cycle.
Results reveal asymmetric directional interactions between motor and somatosensory cortices that are time-locked to rhythmic jaw movement. rM1 emerged as a predominantly self-driven motor output hub while somatosensory regions were network-driven, and cM1 occupied an intermediate sensorimotor integration role. Excitatory drive from cM1 onto rM1U and inhibitory drive from cS1 onto rM1 were both significantly correlated with oral motor kinematics (all spearman $\rho > 0.67$, $p < 0.01$), suggesting complementary feed-forward excitation and sensory-gated inhibition regulating motor output during chewing. The RNN-CURBD framework provides a principled approach for characterizing directed circuit-level interactions from neural population recordings, with broad potential for understanding sensorimotor dysfunction in neurological disease.

Disclosures: E. Tsang: None. **F.I. Arce-McShane:** None.

Poster

PSTR234: Motor Planning and Execution in Humans: Behavior, Neurophysiology, and Imaging

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR234.28/Web Only

Topic: F.04. Voluntary Movements

Support: GR012287

Title: Oral somatosensation shapes cortical encoding of stereotyped tongue movements during natural swallowing

Authors: *S. PUNACHA[1], J.-S. LI[1], D. TANG[2], L. FAVOUR[5], V. HOSACK[3], F. I. ARCE-MCSHANE[4];
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Abstract: Efficient swallowing depends on precisely coordinated and reproducible tongue movements that propel the bolus safely through the oral cavity. These stereotypic movements require integration of tongue biomechanics and somatosensory feedback from the tongue and other oral structures. However, the neural mechanisms that preserve swallow-related movement stereotypy and the consequences of disrupted oral tactile sensation for this coordination remain poorly understood.In this study, we combine high-resolution biplanar videoradiography with chronic multi-electrode recordings from macaque (n=4) orofacial sensorimotor cortex to quantify the organization and cortical representation of three-dimensional tongue stereotypy during swallowing. Radiopaque markers implanted in the tongue allowed us to track tongue movements during swallowing. Control sessions were compared with reversible bilateral trigeminal nerve blocks delivered to sensory nerves to silence tactile sensation in the tongue and surrounding oral structures. This manipulation allowed us to test how loss of oral tactile sensation alters stereotypic tongue movements.We developed a novel kinematic model that quantifies stereotypy by defining how closely each swallow trajectory matches an idealized swallow trajectory using position, direction, and speed similarity indices. Under control conditions, posterior tongue markers followed more stereotypic paths than anterior markers. Oral tactile nerve block preserved the overall swallow pattern but selectively increased stereotypy. To determine how the cortex encodes these movement patterns, the model includes time-resolved mutual information between cortical spiking and the kinematic stereotypy index.This mathematical framework links oral sensation, tongue biomechanics, and cortical activity during natural swallowing, and provides a foundation for understanding how sensory loss may contribute to dysphagia and swallowing impairments in neurodegenerative diseases, including Alzheimer’s disease.

Disclosures: S. Punacha: None. **J. Li:** None. **D. Tang:** None. **L. Favour:** None. **V. Hosack:** None. **F.I. Arce-McShane:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.01/EE27

Topic: F.05. Brain-Machine Interface

Title: Speech restoration using a synthesizer

Authors: *P. R. KENNEDY;
Speech Lab., Neural Speech Inc, Duluth, GA

Abstract: Conversational speech restoration is generally performed by recording single units from the speech cortex, decoding the pattern of neural signal firings using algorithms such as RNN, CNN, SVM, LDA and Transformer and outputting the signals to a large language model (LLM) to interpret the decoded signals and encode speech output. In a recent paper[1], RNN and Transformer decoding were used to decode the pattern of neural signal firings and an LLM was used to produce the speech output with minimal latency between intent to speak and speech output. Hypothesis: It is hypothesized that a simpler system is possible. It consists of connecting identified single units to phonemes so that when the single unit fires it activates the phoneme with output from a synthesizer, thus bypassing the decoding algorithms and LLM.
This hypothesis is open for discussion.
1.Wairagkar M, Card NS, Singer-Clark T, Hou X, Iacobacci C, Miller LM, Hochberg LR, Brandman DM, Stavisky SD. An instantaneous voice-synthesis neuroprosthesis. Nature. 2025 Aug;644(8075):145-152. doi: 10.1038/s41586-025-09127-3. Epub 2025 Jun 12.PMID: 40506548

Disclosures: P.R. Kennedy: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neural Speech Inc..

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.02/EE28

Topic: F.05. Brain-Machine Interface

Support: NIH Grant NS124564
NIH Grant NS131069
NIH Grant NS127849
NIH Grant NS096761
NIH Grant EB029365
Carnegie Mellon University's Center for Machine Learning and Health Fellowship

Title: fMRI-guided contrastive learning improves EEG-only individual-finger BCI decoding

Authors: *J. ZHANG[1], Y. DING[1], Y. ZHANG[1], J. KOSNOFF[1], M. KARRENBACH[2], H. WANG[1], B. HE[3];
[1]Dept. of Biomed. Engin., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Biomed. Engineering, Dept. of Electrical and Computer Engineering, Neuroscienc, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Finger-level motor decoding is an important step toward more naturalistic noninvasive brain-computer interface (BCI) control, yet individual -finger decoding from scalp

electroencephalography (EEG) remains challenging because finger representations are spatially close in the sensorimotor cortex and blurred by volume conduction. Functional magnetic resonance imaging (fMRI) provides high-spatial-resolution maps of finger-specific brain activity, but its high cost and limited temporal resolution make it unsuitable for real-time BCI control. We therefore hypothesize that fMRI-derived spatial information could improve EEG-based finger decoding during training while preserving EEG-only inference. We evaluated EEG decoding of finger movement execution (ME) and motor imagery (MI), with fMRI-derived finger representations used as spatial anchors during training. Models decoded either two finger classes, thumb versus pinky, or three finger classes,: thumb, index, and pinky. We developed a shared-space ensemble (SSE) framework in which EEG features and fMRI-derived finger-specific representations are projected into a shared latent space. A cross-modal contrastive learning module was used to align EEG and fMRI representations from the same finger class while separating representations from different classes. During
inference, decoding relied on EEG alone, with fMRI information incorporated only through the learned shared-space structure. In 12 able-bodied participants, we used a session-wise pseudo-online simulation in which models were trained from session 2 onward using prior-session EEG and group-level fMRI data, with each simulation repeated three times. Compared with EEGNet, a widely used deep learning decoder for EEG-BCI, the fused SSE model significantly improved decoding accuracy across all four task settings. In the ME task, SSE improved 2-class accuracy from 66.10 ± 1.21% to 74.90 ± 1.08% (corrected $p = 0.026$) and 3-class accuracy from 45.48 ± 0.81% to 54.24 ± 0.43% (corrected $p = 0.006$). In the MI task, SSE improved 2-class accuracy from 79.07 ± 1.59% to 85.13 ± 0.47% (corrected $p = 0.026$) and 3-class accuracy from 61.02 ± 0.47% to 70.94 ± 0.40% (corrected $p = 0.006$). The largest gain was observed in the more challenging MI 3-class setting. These findings indicate that fMRI-derived finger prototypes can provide useful spatial constraints for EEG representation learning. SSE improves noninvasive finger-level BCI decoding while preserving EEG-only inference, offering a multimodal strategy for integrating the spatial specificity of fMRI with the real-time applicability of EEG.

Disclosures: J. Zhang: None. **Y. Ding:** None. **Y. Zhang:** None. **J. Kosnoff:** None. **M. Karrenbach:** None. **H. Wang:** None. **B. He:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.03/EE29

Topic: F.05. Brain-Machine Interface

Support: Japan Science and Technology Agency (JST), FOREST, JPMJFR206G
Japan Society for the Promotion of Science (JSPS) KAKENHI, 24K02990

Title: Kinesthetic motor imagery predicts brain-computer interface performance, whereas vibration-induced facilitation occurs only in high-performing users

Authors: *K. KASAHARA, R. OHKUMA, T. TANABE, K. HIKISHIMA;
Natl. Inst. of Advanced Industrial Sci. and Technol. (AIST), Tsukuba, Ibaraki, Japan

Abstract: Motor imagery-based brain-computer interfaces (MI-BCIs) show interindividual variability in performance, which hinders their practical application. Our previous studies demonstrated that MI-BCI performance is associated with the cortical volume of motor-related regions and the functional connectivity of the motor cortex-basal ganglia network, suggesting that individual differences in motor representations and motor network function contribute to BCI aptitude. Previous studies have also suggested that kinesthetic motor imagery plays an important role in successful MI-BCI control. However, although the relationship between kinesthetic imagery and MI-BCI performance has become increasingly evident, whether interventions designed to facilitate kinesthetic sensations can improve MI-BCI performance remain unclear.

Fifty-three healthy participants performed an MI-BCI task in which they controlled the interface using imagined hand tapping. Participants received no explicit instructions about the use of kinesthetic or visual motor imagery. After the experiment, they rated their imagery style using a Kinesthetic-Visual Imagery Scale ranging from 0 (purely visual imagery) to 100 (purely kinesthetic imagery), with 50 indicating equal reliance on both strategies. MI-BCI performance was positively correlated with kinesthetic imagery preference ($r = 0.36$, 95% CI [0.10, 0.58], $p = 0.007$).

To investigate whether kinesthetic sensations can facilitate MI-BCI control, vibration stimulation was applied to evoke an illusion of hand movement during MI-BCI operation. Eleven participants were classified as high-performing (baseline accuracy ≥63.5%, n = 6) or low-performing (baseline accuracy <63.5%, n = 5). Changes in MI-BCI performance were normalized to each participant's baseline performance, which was set at 100%. Vibration stimulation significantly increased normalized performance in the high-performing group ($p < 0.05$), whereas no significant effect was observed in the low-performing group.

These findings suggest that greater reliance on kinesthetic imagery is associated with better MI-BCI performance. However, vibration-induced movement illusion improved performance only in participants with relatively high baseline aptitude and failed to enhance performance in low-performing participants. The results suggest that sensory facilitation alone may be insufficient to overcome poor MI-BCI performance. Further studies are needed to identify factors that limit MI-BCI performance in low-performing participants and to develop effective interventions for improving BCI control.

Disclosures: K. Kasahara: None. **R. Ohkuma:** None. **T. Tanabe:** None. **K. Hikishima:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.04/EE30

Topic: F.05. Brain-Machine Interface

Support: NIH Grant NS124564
NIH Grant NS131069
NIH Grant NS127849
NIH Grant NS096761

Title: Sensory-guided human-machine joint learning accelerates the acquisition of motor imagery brain computer interface control

Authors: *H. WANG[1], Y. ZHANG[1], M. KARRENBACH[1], Y. DING[1], B. HE[2];
[2]Dept. of Biomed. Engin., [1]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Motor imagery brain-computer interfaces (MI-BCIs) offer a non-invasive pathway for communication and neurorehabilitation [1], yet their practical use remains limited by slow user learning and unstable decoder adaptation. A key challenge is that the human learner and machine decoder typically adapt independently, resulting in inefficient co-adaptation. Here, we present a sensory-guided human-machine joint learning framework that treats MI-BCI training as a coordinated two-learner problem: vibrotactile guidance shapes neural representations, while adaptive decoder reweighting reinforces separable EEG features.
31 BCI-naïve participants were assigned to a joint learning group (n = 15), a tactile control group (n = 8), or a conventional BCI2000 control group (n = 8), and completed longitudinal EEG-based 1D and 2D cursor-control training. Joint learning resulted in superior MI-BCI performance. In 1D/2D tasks, the joint learning group achieved 86.0%/77.5% percent valid correct and 84.2%/75.2% forced percent total correct, with 77.5%/66.9% continuous online accuracy. Baseline performance did not differ across groups, indicating improvements were training-induced. Left/right online accuracy increased by 19.0% following joint learning, compared to 6.3% in the tactile control group and 3.0% in the BCI2000 control group. Joint learning produced stronger alignment between neural signal changes and decoder gradient directions, indicating convergence toward shared, control-relevant representations. EEG analyses revealed enhanced alpha- and beta-band event-related desynchronization over sensorimotor cortex and more focused, class-specific motor imagery patterns. Correspondingly, decoder weights were preferentially assigned to separable neural features, linking neural discriminability to machine-side optimization. Importantly, these gains were not transient effects of sensory stimulation. Participants in joint learning group maintained performance after tactile guidance was removed and retained superior 1D and 2D control during long-term follow-up without sensory cues. Together, these findings establish sensory-guided joint learning as an effective strategy for synchronizing neural plasticity and machine adaptation. This framework has broad potential for improving assistive communication, robotic control, neurorehabilitation, and scalable human-machine interaction.
[1] Edelman, B. J., Zhang, S., Schalk, G., Brunner, P., Müller-Putz, G., Guan, C., & He, B. (2024). Non-invasive brain-computer interfaces: state of the art and trends. *IEEE reviews in biomedical engineering,* 18, 26-49.

Disclosures: H. Wang: None. **Y. Zhang:** None. **M. Karrenbach:** None. **Y. Ding:** None. **B. He:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.05/EE31

Topic: F.05. Brain-Machine Interface

Support: NIH Grant NS124564
NIH Grant NS131069
NIH Grant NS127849
NIH Grant NS096761
NIH Grant EB029365

Title: EEG Foundation Model Improves Online Directional Motor Imagery Brain-computer Interface Control

Authors: *M. A. KARRENBACH[1], H. WANG[2], Z. JOHNSON[2], Y. DING[2], B. HE[2];
[1]Electrical and Computer Engin., [2]Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Brain-Computer interfaces (BCIs) enable communication between neural activity and external systems, allowing users to control devices for augmenting motor function, as well as enhancing capabilities in broader populations [1]. Electroencephalography (EEG) provides high temporal resolution, making it well suited for providing dynamic, real-time feedback in noninvasive BCI frameworks. However, its practical effectiveness is limited by low spatial resolution and low signal-to-noise ratio, which constrain decoding accuracy and often result in unintuitive control paradigms. In this study, we present a framework for an online EEG foundation model, pretrained with spectrogram reconstruction of compact temporal windows and constraints mimicking online conditions during data preprocessing. We evaluate the model in a challenging control paradigm involving single-arm, directional motor imagery with dynamic cursor movements. For comparison, we include a conventional deep learning architecture (EEGNet) for online decoding, with both models evaluated in a blind, randomized order during each session. In cued experiments with 11 able-bodied participants, the foundation model achieved a final average accuracy of 51.3% ± 5.0 (standard error), outperforming EEGNet (34.2% ± 4.8), corresponding to a 26.3% improvement above chance level. Wilcoxon signed-rank tests confirmed that this improvement was statistically significant ($p=0.0057$). In free movement tasks, where participants performed self-directed trajectories to reach a target, the foundation model yielded higher completion rates and shorter completion times during successful runs. Additionally, the foundation model demonstrated superior adaptability through same-session fine-tuning (7.9% ± 3.1 improvement), compared to minimal gains observed in EEGNet (0.13% ± 1.8). The model also exhibited enhanced capacity to support user learning, as reflected by increased signal discriminability in offline analyses. Together, these findings highlight the potential of EEG foundation models to enable more robust, adaptive, and intuitive noninvasive BCI systems in real-time settings, and provide a promising modelling framework for future BCI development.

References:

[1] Edelman, B. J., Zhang, S., Schalk, G., Brunner, P., Müller-Putz, G., Guan, C., & He, B.

(2024). Non-invasive brain-computer interfaces: state of the art and trends. IEEE reviews in biomedical engineering, 18, 26-49.

Disclosures: M.A. Karrenbach: None. **H. Wang:** None. **Z. Johnson:** None. **Y. Ding:** None. **B. He:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.06/EE32

Topic: F.05. Brain-Machine Interface

Support: PMDC 2024
PMDC 2025

Title: Detecting Freezing of Gait from GPi Local Field Potentials in Parkinson's Disease

Authors: *N. DRUCK[1,2], J. WALLNER[2,1], L. CLOUD[3], K. HOLLOWAY[4], D. J. KRUSIENSKI[2,1];
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Abstract: Freezing of gait (FoG) is among the most disabling symptoms of Parkinson's disease (PD), contributing to falls and loss of independence. Despite its clinical impact, FoG may not respond to medication, and its neural mechanisms remain incompletely understood. Although the globus pallidus internus (GPi) is an established target for deep brain stimulation (DBS), the neural signatures of locomotor states within the GPi remain poorly characterized, as most prior work has focused on the subthalamic nucleus. This gap is relevant because closed-loop DBS must distinguish freezing from voluntary standing rather than simply separating walking from freezing. In addition, phase-amplitude coupling (PAC) has been minimally explored in pallidal recordings. The present work characterizes GPi local field potential (LFP) spectral features across locomotor states and evaluates whether they distinguish walking, standing, and FoG using a three-class machine-learning framework. GPi LFPs were recorded from four PD participants (three male, one female; ages 60-73) implanted with the Medtronic Percept PC while on-medication and off-stimulation during FoG-eliciting walking and intentional standing. LFPs were synchronized with ankle accelerometer and video data. FoG events were annotated in real time and verified using accelerometry. LFPs were segmented into 5-s windows (75% overlap), and eleven features were extracted: relative bandpower in six canonical frequency bands and the modulation indices for five lower-band-gamma PAC pairs. Participant-specific support vector machines were trained using single and combinations of features, respectively. Single-feature models achieved balanced accuracies of 30-67%, whereas combined models achieved a mean balanced accuracy of 80.7% (chance 33.3%), representing an improvement of 12.1-22.5 points over the best single feature. Recall exceeded 73% recall for all locomotor classes. High-beta

power was selected most frequently (70% of folds), consistent with movement-related beta modulation; whereas the other selected features varied across participants, underscoring the importance of individualized feature selection. Three of four participants also exhibited increased lower-frequency-gamma coupling during FoG relative to both walking and standing, suggesting cross-frequency coupling as a
potential freezing-related biomarker. Despite the small sample size and off-stimulation recording condition, these findings demonstrate that GPi LFPs can reliably distinguish FoG from both walking and intentional standing, supporting the feasibility of FoG detection for adaptive GPi-DBS.

Disclosures: N. Druck: None. **J. Wallner:** None. **L. Cloud:** None. **K. Holloway:** None. **D.J. Krusienski:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.07/FF1

Topic: F.05. Brain-Machine Interface

Support: NRF Grant No. 00450314
Alchemist Grant No. 02634714

Title: Apparent regional representation in a multi-region transformer decoder is an artifact of cross-region routing, not local encoding

Authors: *W. CHOI[1], M.-K. KIM[2], S.-H. KIM[3], J.-W. SOHN[5,4];
[1]Dept. of Industrial Engin., Konkuk University, Seoul, Seoul, Korea, Republic of; [2]Div. of Computer Engin. (Artificial Intelligence major), Baekseok Univ., Cheonan-si, Korea, Republic of; [3]Intelligent Precision Healthcare Convergence, [4]Dept. of Global Biomed. Engin., Sungkyunkwan Univ., Suwon, Korea, Republic of; [5]Dept. of Med. Sci., Catholic Kwandong Univ., Gangneung-si, Korea, Republic of

Abstract: Decoding a behavioral variable from a brain region is often read as evidence that the region represents it. This inference is especially fragile for attention-based decoders applied to several regions at once: they pool spikes into a shared latent, so a decoded variable need not originate in any one region, and the attention weights invite over-interpretation. We applied one such decoder (POYO) to a sequential reaching task with an uncued mid-trial target change in two macaques (simultaneous M1 and DLPFC; 210/115 and 147/100 units, 4 and 3 sessions), and found that DLPFC velocity decoding rose after the change—a signal one might read as DLPFC representing the upcoming target. To test this, we classified the second target from raw rates and POYO's 128-d latents (linear and nonlinear, against a label-shuffle null, FDR-corrected), ablated each region by masking its spikes, separated prospective from reactive timing, and compared encoder attention with the decoder pathway from the velocity output to each region (directions

only, as 24 latent layers blur magnitudes). The DLPFC velocity rise was reliable (7/7 sessions, $p<0.02$) but small, far below M1, and reactive—it followed the change rather than preceding it. Raw DLPFC appeared to classify the target (26-90% vs M1's 5-14%), but since the first target partly predicted the second, this was leakage: controlling for the first target, DLPFC fell to near zero and never exceeded M1, and POYO latents agreed (DLPFC 0.478 vs M1 0.544); nonlinear decoders added nothing. Ablation localized velocity to M1—masking M1 collapsed decoding (R^2 0.98→0.47), DLPFC alone gave 0.009, and removing DLPFC was harmless (0.968)—so the DLPFC boost is M1 information routed through the shared latent. Encoder attention to DLPFC rose after the change (6/7 sessions), but the velocity output's decoder pathway to DLPFC did not (it rose in only 2/7 sessions, sign-test $p=0.94$), consistent with the ablation: the encoder reads DLPFC but the readout does not use it. Thus a region from which the target seemed decodable, whose velocity rose at a behaviorally meaningful moment, and which drew the model's attention neither represented the target nor supplied the velocity. Decodability and attention do not establish regional representation; with region-mixing decoders, causal tests and readout-level tracing are required

Disclosures: W. Choi: None. **M. Kim:** None. **S. Kim:** None. **J. Sohn:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.08/FF2

Topic: F.05. Brain-Machine Interface

Support: NIH R61MH135407
NIH R01MH123770
the One Mind Rising Star Award
RF1DA056402
the Foundation for OCD Research (FFOR)

Title: Unified EEG Decoding via Instruction-Tuned Foundation Models

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Abstract: Electroencephalography (EEG) provides a non-invasive window into brain activity and is widely used to study neural processes in both research and clinical settings. Analyzing EEG data typically requires specialized, task-specific architectures that struggle to generalize across diverse recording conditions and applications. Recent EEG foundation models have improved representation learning through large-scale pretraining, but they generally require separate finetuning for each downstream task. To address these limitations, we introduce a unified framework that reformulates neural data decoding as an instruction-conditioned

understanding problem. Our approach transforms raw EEG data into structured representations, allowing a single foundation model to process multiple distinct tasks simultaneously via instruction conditioning. We evaluate our framework across several heterogeneous datasets spanning diverse cognitive and clinical settings. Taken together, our results demonstrate that combining structured representations with instruction-tuned foundation models is a viable mechanism for unified EEG decoding, establishing a scalable path toward universal neural foundation models.

Disclosures: P. Azizeddin: None. **O. Sharafi:** None. **M.M. Shanechi:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.09/FF3

Topic: F.05. Brain-Machine Interface

Support: STI 2030—Major Projects (2021ZD0200404)
National Natural Science Foundation of China (62336007)
Pioneer R&D Program of Zhejiang (2024C03001)
the Starry Night Science Fund of Zhejiang University Shanghai Institute for Advanced Study (SN-ZJU-SIAS-002)
the Fundamental Research Funds for the Central Universities (2023ZFJH01-01, 2024ZFJH01-01)

Title: Cortical representations and shared neural dynamics underlying multidimensional handwriting movements

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Abstract: Handwriting is a uniquely human motor skill, yet the comprehensive cortical representations and neural dynamics that govern this complex motor behavior remain incompletely understood. Here, we investigated these mechanisms by recording intracortical activity from a paralyzed participant attempting to write complex Chinese characters. We first examined the neural encoding of handwriting's two distinct processes: on-paper strokes and in-air pen-lifts. While both exhibited tuning to two-dimensional (2D) velocity, a significant portion of neural variance remained unexplained, leading us to model handwriting as a multidimensional behavior incorporating 3D velocity, grip force, pressure, and electromyographic signals, which were templated from six healthy subjects. Incorporating these additional kinematic and kinetic dimensions significantly improved neuronal encoding models for both strokes and pen-lifts. Furthermore, we explored the neural population dynamics underlying these actions. We discovered that strokes and pen-lifts occupy a shared neural subspace, where a common set of

stable dynamics is differentially activated into distinct regions of state space to generate process-specific patterns. Linear combinations of these dynamics give rise to the movement kinematics and kinetics, with their activation patterns—spanning both output-potent and output-null dimensions—showing greater cross-day stability than raw neural signals. Critically, integrating these multidimensional representations and stable neural dynamics into decoding models led to markedly enhanced performance, including increased recognition rates among multiple complex characters and more accurate, stable decoding of movement trajectories. Together, these results reveal that the motor cortex employs a robust, shared dynamical system to flexibly generate multidimensional handwriting. These insights not only advance our fundamental understanding of motor control but also provide a principled framework for future studies of complex human motor behaviors.

Disclosures: Z. Wang: None. **B. Yu:** None. **Y. Hao:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.10/FF4

Topic: F.05. Brain-Machine Interface

Support: JST Moonshot R&D Grant Number JPMJMS2012 Japan

Title: Resting alpha and beta sensorimotor rhythms may reflect dissociable neural adaptation processes during motor imagery brain-computer interface neurofeedback

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Abstract: Sensorimotor rhythm-based brain-computer interface (BCI) neurofeedback is a promising strategy for motor rehabilitation, yet learning outcomes vary substantially across individuals. It remains unclear whether apparent non-responsiveness reflects genuine learning failure or the limited sensitivity of conventional event-related desynchronization (ERD) metrics. We reanalyzed scalp EEG data from 40 healthy adults who performed kinesthetic motor imagery of right thumb extension during a five-block protocol (pre/post-assessment without feedback; three neurofeedback training blocks). After spectral quality screening, 33 participants were retained. Resting spectral features were quantified using specparam algorithm, and six task-related ERD metrics were computed from electrodes over the contralateral sensorimotor cortex. A data-driven grid-search approach identified baseline features associated with training-related changes.Resting alpha peak power (IAP) was negatively correlated with maximum ERD depth during motor imagery (repeated-measures correlation: $r = -0.490$, $p < 0.001$). Participants with high baseline IAP showed significant ERD deepening during early training (Group × Block: $p = 0.003$, partial $\eta^2 = 0.167$; Block 1 vs. 2: $p = 0.016$, $d = 0.81$), whereas the low-IAP group showed

no significant change. Resting beta peak power (IBP) showed a homeostatic-like, baseline-dependent pattern: participants with low initial IBP exhibited a significant increase from Block 1 to Block 3 (Group × Block: $p = 0.020$, partial $\eta^2 = 0.119$; post hoc $p = 0.018$, $|d| = 0.745$), and baseline IBP was negatively correlated with subsequent change ($r = -0.482$, $p = 0.004$). This pattern did not differ between verum and sham groups, suggesting motor imagery-driven sensorimotor regulation rather than feedback-contingent learning.These findings suggest that alpha and beta rhythms capture dissociable aspects of BCI training: resting alpha power may index inhibitory gating capacity for task-specific ERD generation, whereas beta power may reflect homeostatic-like regulation of cortical excitation-inhibition balance, consistent with GABAergic normalization. These baseline spectral markers may inform individualized stratification of neurofeedback protocols beyond the conventional responder/non-responder dichotomy.

Disclosures: M. Tanaka: None. **S. Iwama:** None. **J. Ushiba:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.11/FF5

Topic: F.05. Brain-Machine Interface

Support: National Science and Technology Major Project of China (2025ZD0217000)
National Natural Science Foundation of China (32371154)
Lin Gang Laboratory (LG-GG-202402-06)

Title: Cross-modal multiband neural decoding of phonological units for Mandarin speech brain-computer interfaces

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Abstract: Speech brain-computer interfaces (BCIs) increasingly aim to restore communication from intracranial neural activity. However, Mandarin Chinese remains challenging due to its dual dependence on syllabic structure and lexical tone, and previous decoding efforts have been largely restricted to a single intracranial modality—either stereo-electroencephalography (sEEG) or electrocorticography (ECoG). Here, we introduce a multiband intracranial electroencephalography (iEEG) framework that represents sEEG and ECoG recordings as channel-by-time-by-band tensors, decoding Mandarin phonological units with a common convolutional neural network (CNN)-Transformer architecture. In five sEEG participants performing isolated-character, isolated tonal-syllable, and continuous sentence reading tasks, tone decoding proved highly robust across subjects, yielding a mean accuracy of 71.2% (against a ~25% chance level). Although decoding initials and finals presented a greater challenge as they

encompassed the full spectrum of Mandarin phonological categories, the model consistently yielded probabilistic candidate distributions that outperformed chance levels by up to 12- and 9-fold—reaching 53.5% and 25.3% accuracy, respectively— supporting downstream reconstruction of syllable sequences. Crucially, band ablation analyses revealed that low-frequency neural activity carried critical complementary information to high-gamma activity, improving decoding beyond high-gamma features alone. Channel-level contribution maps further related task- and band-dependent representations to patient-specific cortical and subcortical electrode coverage. To validate cross-modality generalizability, we applied the identical decoder architecture to Mandarin ECoG recordings, achieving strong decoding performance across syllables, initials, finals, and tones. Finally, fine-tuning phonological-unit decoders trained on isolated reading data with sentence-reading data demonstrated a practical pathway toward continuous Mandarin sentence reconstruction. Together, these results establish a robust, cross-modality phonological unit-decoding strategy for Mandarin speech BCIs.

Disclosures: S. Xiang: None. **Q. Liu:** None. **Y. Cai:** None. **H. Zhang:** None. **Z. Wang:** None. **Y. Li:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.12/FF6

Topic: F.05. Brain-Machine Interface

Support: MJFF-024653
Marco Bonizzato's salary is supported by FRQS
Claire Duusard's salary is supported by FRQS

Title: Decoding freezing of gait in Parkinson’s disease using simultaneous cortical and subcortical electrophysiology

Authors: A. BALACHANDAR[1], *C. DUSSARD[3], D. BURCHIELLI[4], G. SORRENTO[5], S. COLEMAN[6], K. MITHANI[1], G. IBRAHIM[7], S. K. KALIA[8], M. BONIZZATO[9], A. FASANO[2]; [1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Medicine, Div. of Neurol., Univ. of Toronto, Toronto, AB, Canada; [3]Dept. of Electrical Engin., Polytechnique Montréal, Montréal, QC, Canada; [4]Polytechnique Montréal, Montreal, QC, Canada; [5]Movement Disorders, Univ. Hlth. Network, Toronto, ON, Canada; [6]The Hosp. For Sick Children, Toronto, ON, Canada; [7]The Hosp. for Sick Children, Toronto, ON, Canada; [8]Toronto Western Res. Inst., Toronto, ON, Canada; [9]Electrical Engin., Polytechnique Montreal, Montreal, QC, Canada

Abstract: Freezing of gait (FOG) is a disabling episodic gait disturbance in Parkinson’s disease (PD) that often persists despite levodopa and deep brain stimulation (DBS), highlighting the need for neural biomarkers to support future closed-loop therapies. Cortical-subcortical dynamics underlying FOG remain poorly characterized. We tested whether FOG-related neural states can

be decoded from invasive recordings and whether cortical stimulation modulates gait initiation. In this prospective proof-of-concept study, n=3 PD patients with levodopa-partially responsive FOG undergoing clinically indicated subthalamic nucleus (STN) DBS were temporarily implanted with bilateral high-density electrocorticography (ECoG) arrays over motor/premotor cortex between DBS lead implantation and pulse-generator insertion. FOG was recorded both spontaneously and provoked using a virtual-reality split-belt treadmill while cortical and subthalamic local field potentials and synchronized video were recorded. Epochs were visually labeled as non-FOG, pre-FOG or FOG. In the first participant, we extracted 1-s band-power features every 100 ms from 64 ECoG and 16 STN channels. In the pilot participant, cortico-subthalamic imaginary coherence increased in the alpha band (8-13 Hz) during FOG between left somatosensory cortex and left STN ($p=0.047$), and between left premotor cortex and left STN ($p=0.047$). A self-supervised contrastive model (CEBRA) separated FOG from non-FOG epochs (Cohen's $d=2.64$, $p<0.001$) and pre-FOG from non-FOG epochs ($d=2.19$, $p<0.001$), while pre-FOG and FOG overlapped ($d=0.06$). An offline supervised XGBoost binary FOG classifier trained on band-power features with leave-one-recording-out cross-validation and medication-state-specific models detected FOG with $F1=0.72$, balanced accuracy=0.667 and precision-recall $AUC=0.682$.
These preliminary findings suggest that invasive cortical-subcortical recordings can capture pre-FOG/FOG neural states and may guide the development of closed-loop cortical stimulation for PD gait dysfunction.

Disclosures: A. Balachandar: None. **C. Dussard:** None. **D. Burchielli:** None. **G. Sorrento:** None. **S. Coleman:** None. **K. Mithani:** None. **G. Ibrahim:** Other; received honoraria and/or research support from Abbott, Boston Scientific, and Medtronic.. **S.K. Kalia:** None. **M. Bonizzato:** Other; co-inventor of active patents US10279167 and CA3146323 for devices enabling spinal and cortical neuromodulation of gait. M.B. is also co-founder of 12576830 Canada Inc. **A. Fasano:** Other; received honoraria and/or research support from Abbott, Boston Scientific, and Medtronic.

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PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.13/FF7

Topic: F.05. Brain-Machine Interface

Support: NIH R01DA063389
NSF Grant 2223822

Title: Probabilistic Neural Sequences for Adaptive Decoding of Behavior

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Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Decoding behavior from neural populations is crucial to understanding sensorimotor computation. However, modeling the relationship between neural activity and behavior can be challenging due to the often nonlinear and degenerate latent structure of these computations. The efficacy of such decoders is also limited by temporal instability and distributional shifts between contexts or tasks. We present a novel streaming algorithm that learns patterns in latent neural activity and predicts behavior through a probabilistic sequence decoding (PSD) framework. PSD constructs probabilistic neural states via emission probabilities of adaptive gaussian nodes fit to the neural data. These states are then concatenated across time to form temporal sequences. As sequences are observed during training, PSD learns a dictionary of distinct sequences and their behaviors. To predict behavior, observed sequences are matched to those in the dictionary. PSD then uses an exponential weighted average to interpolate between behaviors assigned to similar sequences. Through this process, PSD is able to adapt to nonstationarities in the neural data and continuously decode behavior in real time.
We evaluate performance on simulated datasets and two experimental datasets containing spiking activity while a non-human primate performs a motor task, MC Maze (Pei et al. 2021) and LINK (Temmar et al. 2025). In simulation, PSD and neural network decoders outperform linear models on degenerate neural data, indicating that nonlinear models resolve degeneracy better than linear models. On experimental data, PSD outperforms the linear model but underperforms the neural network model. However, the neural network's performance comes at the cost of 3 times as many parameters. We demonstrate that PSD achieves its core goal of generalization; unlike traditional static models, PSD can flexibly adapt to ongoing distributional shifts. When synthetic rotational drift is applied to the MC Maze dataset, PSD maintains decoding performance at up to 180 degrees of drift while the linear and neural network models fail by just 60 degrees. We also demonstrate that when trained on multiple datasets with distinct neural-behavioral relationships, PSD achieves comparable or better predictions than the linear or neural network models. Finally, we demonstrate that PSD is highly interpretable, allowing for the discovery and investigation of neural trajectories on non-stereotyped data such as a mouse during foraging behavior (Zong et al. 2022). Through probabilistic modeling of neural dynamics as sequences, PSD provides an interpretable model for decoding behavior from neural populations.

Disclosures: R.I. Parsons: None. **H. Temmar:** None. **A. Draelos:** None.

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PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.14/FF8

Topic: F.05. Brain-Machine Interface

Support: FWO (G014126N)
KU Leuven grant (C14/22/134)

Title: Environmental complexity reveals distinct contributions of primary motor and premotor cortex to adaptive control in brain-machine interface in nonhuman primates

Authors: *A. SEPE[1], S. DE SCHRIJVER[2], I. CAPRARA[1], O. SAUSSUS[1], R. DETRY[1], P. SONG[1], T. DECRAMER[1], P. JANSSEN[1];
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Abstract: Motor brain-machine interfaces (BMIs) provide a unique framework for investigating how cortical populations support goal-directed behavior by enabling tests of the direct contribution of different brain regions to motor control. However, most BMI studies have focused on simple environments, leaving unresolved how motor and premotor circuits contribute as environmental demands increase.
We recorded neural activity simultaneously from primary motor cortex (M1), ventral premotor cortex (PMv), and dorsal premotor cortex (PMd) using three 96-channel Utah arrays implanted in macaques performing BMI control in immersive 3D virtual environments. Neural activity was decoded online to control an avatar navigating toward visual targets. Tasks varied in environmental complexity, ranging from simple target-directed movements in an empty environment to conditions requiring continuous adaptation to obstacles, changing viewpoints, and cluttered scenes.
Across all tasks, monkeys achieved stable performance using a decoder trained using only passive observation of a simple target-directed movement. During BCI control in environments with unexpected perturbations (i.e., obstacle appearance), M1 and PMd activity were minimally affected, whereas PMv exhibited robust modulation following environmental changes.To characterize population dynamics across environments, we applied Gaussian Process Factor Analysis (GPFA) to simultaneously recorded units across different tasks. Neural trajectories remained globally conserved across tasks but underwent area-specific geometric transformations. Increasing environmental complexity was associated with higher-dimensional population dynamics in PMv and PMd, whereas M1 activity became progressively lower-dimensional and dominated by changes in trajectory offset rather than geometry.Finally, we assessed the contribution of each area by selectively removing its activity from the decoder. M1 activity alone was sufficient to support performance in simple environments, whereas successful adaptation to environmental demands increasingly relied on premotor activity.
These findings suggest that increasing environmental complexity progressively shifts neural control from motor execution signals in M1 toward premotor activity that supports adaptive control and flexible interactions with the environment.

Disclosures: A. Sepe: None. **S. De Schrijver:** None. **I. Caprara:** None. **O. Saussus:** None. **R. Detry:** None. **P. Song:** None. **T. Decramer:** None. **P. Janssen:** None.

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PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.15/FF9

Topic: F.05. Brain-Machine Interface

Title: Interpretable decoding of reach kinematics from ECoG using a CNN-Transformer-LSTM model

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Abstract: Decoding continuous arm kinematics from cortical activity is a central goal of brain-machine interface (BMI) research, but existing deep learning models often provide limited insight into the neural features that support decoding. Here, we developed an interpretable CNN-Transformer-LSTM architecture for reconstructing naturalistic reaching movements from electrocorticography (ECoG). ECoG data were recorded from three epilepsy patients implanted with high-density grids over frontal, sensorimotor, and parietal cortical regions. The model predicted three-dimensional trajectories of the shoulder, elbow, wrist, and index finger. Interpretability was built into the model by constraining the feature-extraction pipeline to (a) training the model to estimate the forward matrix that extracts component-specific activity from channel space and (b) using learnable wavelet-like convolution to extract the power over task-specific frequencies. Such approaches allow for analyzing learned spatial and temporal filters after training (Petrosyan et al., 2021). Decoding performance was strongest for grids covering the motor and premotor cortex of the contralateral hemisphere, with correlations exceeding 0.8 in the best-performing participant/grid. Predictions from electrode arrays implanted on the ipsilateral hemisphere remained near chance. Spatial pattern analysis verified that informative weights were concentrated over sensorimotor and premotor regions. Temporal pattern analysis revealed two dominant sources of decoding information: a low-frequency component in the 5-20 Hz range and a high-gamma component centred around 60-80 Hz. The high-gamma contribution was most evident in grids spanning motor and ventral cortical regions, whereas the frontal grid was dominated by the slower component. Together, these findings show that accurate reconstruction of whole-arm reaching kinematics from ECoG can be achieved with a model that remains anatomically and spectrally interpretable, linking BMI performance to plausible neural mechanisms of movement control. This research is supported by funding from the Connected Minds Program (CFREF).

Disclosures: P. Georgiadis: None. **A. Karimi:** None. **O. Flouty:** None. **V. Bharmauria:** None. **D.B. Tweed:** None. **J. Crawford:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.16/FF10

Topic: F.05. Brain-Machine Interface

Support: JST Moonshot R&D Grant Number JPMJMS2012 Japan

Title: Effects of Repetitive Motor Imagery Training Aided by Sensorimotor Rhythm Neurofeedback on Neural Circuit Activity in Motor-Related Brain and Spinal Cord Regions: A Preliminary Experiment

Authors: *M. SHIMMURA[1], M. TANAKA[2], K. HASEBE[3], K. TOMEI[4], K. TSUJIMOTO[7], K. SAJIMA[8], S. VAHDAT[10], M. ABE[9], S. IWAMA[5], J. USHIBA[6];
[1]Grad. school of Sci. and Technology, Keio Univ., Kouhoku-ku, Yokohama, Japan; [2]Grad. Sch. of Sci. and Technology, Keio Univ., Hiyoshi, Kohoku-ku, Yokohama, Japan; [3]Grad. Sch. of Sci. and Technology, Keio Univ., Tokyo, Japan; [4]Keio Univ., Yokohama,Kanagawa, Japan; [5]Grad. Sch. of Sci. and Technol., Keio Univ., Yokohama, Japan; [6]Keio Univ., Kanagawa, Japan; [7]Advanced Neuroimaging, Natl. Ctr. of Neurol. and Psychiatry, Kodaira, Japan; [8]Natl. Ctr. of Neurol. and Psychiatry, Kokubunji City, Tokyo To, Japan; [9]Integrative Brain Imaging Ctr., Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [10]Univ. of California Riverside, Riverside, CA.

Abstract: Commands for voluntary movement are sent to muscles via the corticospinal tract, which descends from the primary motor cortex to the spinal cord. Even without overt movement, neurofeedback training (NFT) combined with kinesthetic motor imagery has been shown to enhance corticospinal excitability. However, region-specific functional changes across the entire spinal cord remain poorly understood, owing to the technical difficulty of spinal fMRI acquisition and analysis, and the challenge of detecting signal changes during motor imagery. The present study hypothesized that NFT based on motor imagery promotes plastic reorganization of the motor command pathway including the spinal cord, and tested this hypothesis by evaluating changes in spinal cord activity during motor imagery using simultaneous brain-spinal cord MRI data.Eight healthy right-handed adults (aged 22-25 years) participated in the study. Participants underwent NFT involving right-hand motor imagery over two consecutive days, and brain-spinal cord MRI was acquired before, immediately after, and one week following the intervention. Data were analyzed using the FASB pipeline. The C7-C8 spinal segments were defined as regions of interest (ROI), and β-values were estimated separately for the dorsal and ventral horns using a general linear model (GLM).Within-subject analyses revealed progressive increases in signal intensity and shifts in cluster localization during both motor execution and motor imagery across sessions. ROI-based analysis of mean β-values showed a significant main effect of day exclusively in the dorsal horn ROI during motor imagery ($F(2, 13.26) = 5.566$, $p < 0.05$). Post-hoc testing indicated that mean β-values at Day 3 were significantly higher than those at Day 1 ($z = 2.81$, $p < 0.05$) and Day 2 ($z = 3.03$, $p < 0.01$). Activity changes in the dorsal spinal horn during motor imagery may reflect modulation of afferent input processing via descending regulation from networks including the primary somatosensory cortex, which is engaged during motor imagery. The delayed emergence of significant β-value enhancement at Day 3 suggests that the learning effects induced by NFT stabilized at the neural circuit level over the one-week interval, ultimately becoming detectable across participants.Repetitive motor imagery training significantly enhanced dorsal spinal horn activity, indicating that descending regulation by a somatosensory-related network engaged during motor imagery is reflected in spinal cord activity. These findings suggest that motor-imagery-based training can induce functional changes not only at the cortical level but also within the spinal cord.

Disclosures: M. Shimmura: None. **M. Tanaka:** None. **K. Hasebe:** None. **K. Tomei:** None. **K. Tsujimoto:** None. **K. Sajima:** None. **S. Vahdat:** None. **M. Abe:** None. **S. Iwama:** None. **J. Ushiba:** None.

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PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

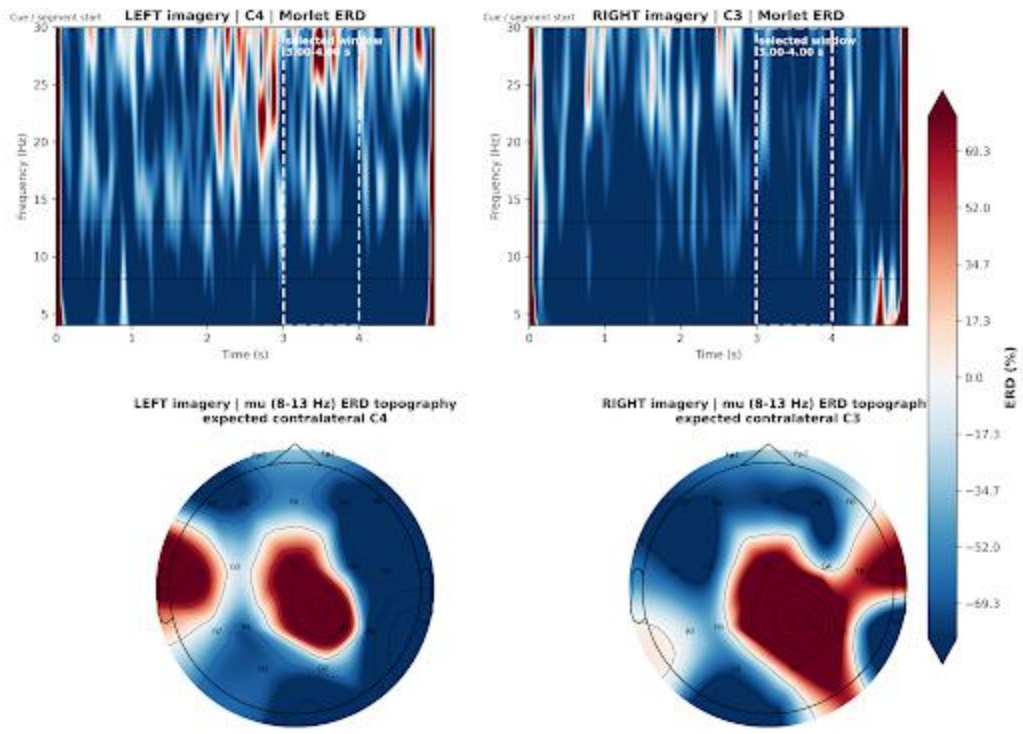
Program #/Poster #: PSTR235.17/FF11

Topic: F.05. Brain-Machine Interface

Title: Artifact-aware EEG motor-imagery decoding for confidence-gated assistive robot control

Authors: *Z. MALIK[1], C. PARK[4], C. SANT'ANA MORVAN[2], I. SMETANA[2], S. SONG[3], S. VARSHAPALLY[2];
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Abstract: Brain-machine interfaces may provide an automated access pathway for individuals with impaired communication or mobility. We developed an exploratory EEG motor-imagery decoding pipeline for confidence-gated control of an assistive robot prototype. One healthy adult female volunteer who provided informed consent (18-35 yr; sex differences not assessed) completed prompted LEFT and RIGHT hand-pressure imagery. Motor imagery was expected to regulate sensorimotor rhythms over central electrodes, specifically through mu/beta event-related desynchronization (ERD) contralateral to the imagined hand. Therefore, the decoder emphasized baseline-normalized ERD and motor-band features from late imagery windows. Trials included target fixation, imagined action, and rest periods. The segments were screened for blink/eye-movement, frontal low-frequency, muscle-like high frequency, global RMS, and amplitude-shift artifacts. A balanced dataset of 52 quality control-accepted trials (26 LEFT/26 RIGHT) was evaluated with a linear support vector machine and stratified cross-validation. The best offline model used the final 1.0 s window and achieved 75.0% accuracy, 75.0% balanced accuracy and 74.9% macro F1, with 39/52 predictions correct (two-sided binomial test vs. 50% chance, p=0.00041). A confidence-gated command layer was implemented to reject uncertain predictions before robot mobilization, and a live prompted test was attempted. Online performance decreased under low-concentration conditions and is treated as a failure mode rather than final efficacy evidence. These results suggest that subject-specific ERD features can support high-chance bidirectional motor-imagery decoding for assistive BMI control, while emphasizing that online adaptation, larger participant samples, and patient testing are required before clinical translation. Figure 1. LEFT/RIGHT motor-imagery ERD patterns. Spectrograms and topographies show contralateral sensorimotor ERD, supporting late-window ERD and C3/Cz/C4-centered intent features.



Disclosures: Z. Malik: None. **C. Park:** None. **C. Sant'ana Morvan:** None. **I. Smetana:** None. **S. Song:** None. **S. Varshapally:** None.

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PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.18/FF12

Topic: F.05. Brain-Machine Interface

Support: This study was supported by JST Moonshot R&D Grant Number JPMJMS2012 Japan.

Title: Connectome-informed deep learning identifies connectome-aligned EEG components during motor imagery neurofeedback

Authors: *K. TOMEI[1], S. IWAMA[2], J. USHIBA[3];
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Abstract: Neurofeedback training (NFT) enables volitional modulation of neural activity and has been applied to brain-machine interfaces and motor rehabilitation. Functional and structural

networks associated with NFT learning have been studied, but how EEG activity during NFT relates to the structural connectome remains poorly understood. Here, we characterized structure-function coupling features of EEG during motor imagery (MI) NFT using a connectome-informed deep learning model. We analyzed high-density EEG and diffusion MRI data from 31 participants after quality control. EEG signals were source-localized and parcellated into 68 cortical regions, and three NFT sessions were used for MI versus relaxation classification. From diffusion MRI-derived connectomes, we constructed graph spectral bases ordered by structural alignment and grouped them into a filter bank spanning structure-coupled to structure-decoupled components. We developed an EEGNet-derived network in which the spatial convolution layer was replaced with a connectome-spectral filter-bank convolution, enabling region-wise learning of structure-function coupling weights. The model outperformed the EEG-only baseline (77.8% vs. 72.3%; main effect of Model: $F(1,29) = 16.34$, $p < 0.001$), suggesting that the structural connectome provided an effective inductive bias for task-relevant EEG features. To test whether this improvement depended on real connectome topology, we compared the model with surrogate graphs preserving degree, strength, edge-weight distribution, or sign-randomized graph spectral bases. The real-connectome model outperformed all surrogate models (paired t-tests, all uncorrected $p < 0.05$), suggesting that MI-NFT-related EEG dynamics were better captured by connectome-specific spectral structure than by generic graph statistics. Learned region-by-filter weights suggested that structure-coupled components contributed in contralateral motor and temporoparietal regions and bilateral posterior cingulate cortex, whereas moderately structure-coupled components involved precuneus, cingulate, and orbitofrontal regions. Preliminary network correspondence analysis suggested that the most structure-coupled filter overlapped with somatomotor/motor networks, whereas an intermediate-coupling filter overlapped with default-mode and frontoparietal networks. These findings suggest that MI-NFT involves EEG features differentially aligned with the structural connectome and demonstrate that connectome-informed deep learning can provide an interpretable approach for exploring structure-function coupling during NFT.

Disclosures: K. Tomei: None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time):; representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources..

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.19/FF13

Topic: F.05. Brain-Machine Interface

Support: This study was supported by JST PRESTO Grant Number JPMJPR23I1 Japan.

Title: Effectiveness of Scalp EEG-Based Neurofeedback Training During Pedaling Motor Training in Humans

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Abstract: Motor imagery is a covert motor process in which specific movements are internally simulated without overt motor output and is known to contribute to motor learning and motor control. Neurofeedback training (NFT), which provides real-time feedback of neural activity during motor imagery, has recently attracted attention as a method for facilitating self-regulation of motor-related brain activity. Although previous studies have demonstrated the effectiveness of NFT mainly in simple movements such as finger movements, it remains unclear whether similar effects can be achieved for complex multi-joint movements. The present study aimed to examine whether NFT targeting alpha-band event-related desynchronization (ERD) enables self-regulation of motor-related brain activity during pedaling motor imagery, a cyclic lower-limb multi-joint movement. Healthy adults completed a single-day NFT intervention consisting of six blocks. During NFT, alpha-band ERD, which is associated with primary motor cortex excitability, was presented as visual feedback. Kinematic performance was also assessed from recorded videos by estimating joint positions. Blocks 1-2, 3-4, and 5-6 were defined as Early, Middle, and Late phases, respectively. A linear mixed-effects model revealed a significant increase in alpha-band ERD across training phases ($F(2, 32.00) = 4.622$, $p = 0.017$). Post-hoc pairwise t-tests with holm correlation further showed that ERD was significantly greater in the Late phase than in the Early phase ($z = 2.902$, $p = 0.011$, $d = 0.704$), suggesting that participants learned to self-regulate the targeted neural activity through NFT. In addition, a correlation analysis showed a significant association between ERD and a kinematic measure under a specific condition (Spearman's $\rho = 0.517$, $p = 0.0377$), indicating that changes in neural activity may covary with motor performance. These findings suggest that NFT targeting alpha-band ERD can facilitate neural self-regulation during pedaling motor imagery and may contribute to condition-dependent improvements in lower-limb motor control.

Disclosures: A. Hasegawa: None. **S. Iwama:** None. **J. Ushiba:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.20/FF14

Topic: F.05. Brain-Machine Interface

Support: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2025-00515593)

Title: Temporal alignment improves MEG-based acoustic reconstruction during natural speech listening

Authors: *G. LEE, J. KIM;
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Abstract: Reconstructing acoustic representations from MEG signals during continuous speech listening is essential for non-invasive speech BCIs. Incorporating temporal flexibility into learning objectives can account for neural variability. Here, we evaluate objective functions using the Gwilliams et al. (2022) dataset, selecting participant S26 a priori based on preliminary decoding peaks. Neural signals comprised 120-Hz downsampled 208-channel MEG signals with a 150-ms temporal offset. The acoustic target was a 120-bin log-mel spectrogram. Utilizing a BiLSTM architecture, we compared a framewise L2 loss baseline (MSE) against a Soft-DTW loss model utilizing a squared Euclidean local cost. Models were evaluated on an unseen test set using DTW-aligned correlation (R_{DTW}), R_{raw}, and alignment path geometry. To characterize local temporal adjustments, we performed post hoc event-instance analyses in paired asymmetric windows immediately before and after phonetic events (-100 to 0 ms and 0 to +100 ms) to quantify alignment gains and event-locked signed path displacement. Soft-DTW improved mean R_{DTW} from 0.6340 to 0.6658 (bootstrap 95% CI [+0.0277, +0.0356]), outperforming the baseline in 68.4% of segments. Conversely, R_{raw} decreased from 0.6085 to 0.4697 (bootstrap 95% CI [-0.1430, -0.1349]). Global path analysis showed a small mean signed offset (+11.53 ms) and a slope near unity (0.9895), arguing against global rescaling. Notably, post-event alignment gains survived multiple-comparison correction (Bonferroni-corrected); distinct incremental gains were captured for vowel-to-consonant transitions (+0.0219) and nasal onsets (+0.0468). In the corresponding post-event windows, Soft-DTW paths stabilized at a clear, localized positive displacement of +17 to +25 ms. By introducing Soft-DTW, we successfully captured flexible correspondences in speech reconstruction without inducing global spatiotemporal rescaling. Crucially, distinct post-event gains immediately following specific phonetic landmarks suggest an intrinsic temporal pace discrepancy between physical acoustic pace and cortical phonetic integration. This implies that rigid framewise constraints obscure cortical temporal flexibility and highlights the need to accommodate these asymmetric dynamics in future phonetic decoder designs. Future work will involve perceptual tests to validate whether this localized geometric realignment enhances intelligibility.

Disclosures: G. Lee: None. **J. Kim:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.21/FF15

Topic: F.05. Brain-Machine Interface

Support: FDT202604051766

Title: Neuronal Avalanches to improve BCI control: from neurophysiological to brain network features

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Abstract: Neuronal avalanches are transient cascades of burst activity that propagate across brain regions, offering a dynamic, network-level view of neural communication. This approach is relevant for motor imagery and motor disorders, which depend on coordinated system dynamics rather than local spectral power changes. Unlike conventional analyses, avalanche-based measures capture aperiodic events treated as noise and model how activity spreads between regions.We investigated neuronal avalanches as biomarkers and decoding features in EEG/MEG studies of motor imagery, BCI learning, and amyotrophic lateral sclerosis (ALS). In a longitudinal EEG motor-imagery BCI study, avalanche length and activation distinguished rest from motor imagery, indexed task engagement, and tracked learning. They correlated with BCI performance and predicted future success with accuracies up to 91%, enabling early identification of users at risk of BCI inefficiency, which affects 15-30% of individuals. Neuronal avalanches thus emerge as biomarkers of individual learning trajectories, enabling personalized BCI training instead of one-size-fits-all protocols. We then tested whether avalanche propagation patterns could support brain-state classification. The Avalanche Transition Matrix (ATM) estimates the probability that activation in one region is followed by activation in another, producing maps of motor-network dynamics. In sensor and source space, ATM-based classifiers outperformed Common Spatial Patterns, particularly in source space (ATM: 80% ± 8%; CSP: 75% ± 14%), while reducing inter-subject variability. Extending this framework to ALS, the Weighted-Stochastic Avalanche Transition Matrix (ws-ATM) captured transition strength and duration while down-weighting short, artifact-driven events. In MEG data, ws-ATM detected network reorganization, correlated with clinical severity, and achieved reliable estimates using ~65% fewer avalanches, supporting shorter recordings in fragile patients.Finally, graph measures from avalanche-based networks, including node strength, communicability, and efficiency, detected task and training effects across sessions and enabled cross-session classification using previous sessions for calibration. Together, these studies establish neuronal avalanches as a framework for mapping motor-network propagation in health, learning, and disease, with relevance for adaptive BCIs and biomarkers of motor neurodegeneration.

Disclosures: C. Mannino: None. **A. Longhena:** None. **M. Corsi:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.22/FF16

Topic: F.05. Brain-Machine Interface

Support: ST Moonshot R&D Grant Number JPMJMS2012 Japan

Title: Neural responsiveness trial of scalp EEG-based neurofeedback intervention for task-specific focal dystonia

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Abstract: Task-specific focal dystonia (TSFD) is a movement disorder characterized by involuntary, sustained muscle contractions occurring exclusively during skilled, task-specific actions such as writing, typing, and playing musical instruments. Sensorimotor network abnormalities have been implicated in its pathophysiology, particularly involving circuits that connect the basal ganglia, thalamus, and cerebral cortex; however, current treatments remain largely symptomatic. Neurofeedback training (NFT) enables volitional self-regulation of cortical activity via real-time scalp EEG feedback and has shown promise as a potential disease-modifying intervention for dystonia. However, whether TSFD patients can effectively engage NFT's learning mechanism remains unknown, given the underlying sensorimotor network dysfunction. Here, we conducted a two-arm parallel-group controlled trial comparing scalp EEG self-regulation capacity during NFT between TSFD patients (n = 12; affected tasks: writing, typing, piano, saxophone) and healthy controls (n = 14). Participants underwent a 45-minute NFT session using motor imagery of the affected hand to induce event-related desynchronization (ERD) in the beta band (26-30 Hz) over the contralateral sensorimotor cortex. Scalp EEG was analyzed across three learning stages (Early, Middle, Late) using event-related spectral perturbation (ERSP). Motor function (Burke-Fahn-Marsden Dystonia Rating Scale Movement; BFMDRS Movement) and psychological state (Beck Anxiety Inventory; BAI, Beck Depression Inventory; BDI) were assessed before and after the intervention. Repeated-measures ANOVA on ERSP revealed no significant main effect of group ($F(1,24) = 0.148$, $p = 0.704$, *partial* $\eta^2 = 0.006$) and no group × stage interaction ($F(2,48) = 0.173$, $p = 0.841$, *partial* $\eta^2 = 0.007$). To confirm the null results, Bayesian independent-samples *t*-tests were conducted, providing evidence for the absence of group differences in ERSP across all learning stages ($BF_{01} = 2.48$-2.74). Following the intervention, anxiety (BAI: $W = 21.00$, $z = 2.201$, $p = 0.031$, $BF_{10} = 5.89$) and depression (BDI: $W = 28.00$, $z = 2.366$, $p = 0.021$, $BF_{10} = 11.86$) scores were significantly reduced. BFMDRS Movement showed a trend toward improvement ($W = 15.00$, $z = 2.023$, $p = 0.054$, $BF_{10} = 2.34$). These results demonstrate that TSFD patients retain neural substrates for scalp EEG self-regulation equivalent to healthy controls, despite sensorimotor network dysfunction. Acute improvements in psychological state and the trend toward motor recovery following a single session suggest that NFT may constitute a viable neuromodulatory intervention for TSFD.

Disclosures: R. Kajihara: None. **M. Murakami:** None. **S. Iwama:** None. **J. Ushiba:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.23/FF17

Topic: F.05. Brain-Machine Interface

Support: This study was supported by JST PRESTO Grant Number JPMJPR23I1 Japan.

Title: Neural representations of an artificial hand become more self-like through BCI training during motor observation

Authors: *R. KAJIHARA[1], T. SERI[2], S. IWAMA[3], J. USHIBA[4];
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Abstract: Title Neural representations of an artificial hand become more self-like through BCI training during motor observation
Authors: Ryogo Kajihara[1],Taiga Seri[1], Seitaro Iwama[2], Junichi Ushiba[21]Graduate School of Science and Technology, Keio University, Japan; [2]Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Japan
AbstractThe human brain can flexibly update body-related representations through tool use and prosthetic experience. However, it remains unclear whether short-term brain-computer interface (BCI) training, performed without overt physical movement, can alter the neural representation of an artificial hand. Here, we examined whether BCI training induces changes in the representational relationship between an artificial hand and the participant's own hand. Seventeen participants completed short-term BCI training in which they learned to operate one type of on-screen artificial hand using their brain activity. Before and after training, EEG was recorded while participants performed motor observation and motor imagery tasks under three visual conditions: their own hand, the trained artificial hand, and an untrained artificial hand. Representational similarity analysis (RSA), which quantifies the similarity of multivariate neural activity patterns across conditions, was applied to EEG activity over motor-related regions, and the representational distance between each artificial hand and the participant's own hand was computed using cosine distance. During motor observation, the representational distance between the trained artificial hand and the participant's own hand significantly decreased after BCI training ($p < 0.05$, paired t-test), whereas no significant change was observed for the untrained artificial hand. No significant training-related changes were found during motor imagery. These findings demonstrate that even brief BCI-mediated experience is sufficient to induce functional adaptation in the neural representation of an artificial hand, indicating that short-term training can reorganize sensorimotor representations and that the human brain can rapidly integrate artificially controlled effectors into existing body-related networks.

Disclosures: R. Kajihara: None. **T. Seri:** None. **S. Iwama:** None. **J. Ushiba:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.24/FF18

Topic: F.05. Brain-Machine Interface

Title: Demultiplexing attempted movement and touch from a sensorimotor ECoG array in incomplete tetraplegia: perceived and non-perceived stimuli

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Abstract: Motor commands and the sensory information of touch are intermingled within the sensorimotor cortex, yet brain-computer interfaces (BCIs) after spinal cord injury have largely exploited mainly the motor component. Whether both streams can be read out simultaneously from a single cortical interface, and whether touch is still processed cortically even where it is no longer perceived, is unclear. Decoding such tactile signals, including ones below the perceptual threshold, could be used either to improve motor decoding or to inform future sensory-feedback strategies. We asked whether attempted movement and passive touch can be jointly decoded and demultiplexed from a single epidural ECoG array (WIMAGINE, Clinatec; clinical trial NCT02550522) spanning S1/M1, and how decoding differs between skin regions with and without residual sensation. Here we show, in a participant with chronic incomplete C6 tetraplegia and residual proximal arm function, that grasp type and tactile stimuli (light or strong) are decoded well above chance, both in isolation and when motor and sensory events co-occur. Combined trials remained decodable, although with reduced accuracy relative to single-condition trials, indicating that motor and sensory streams can still be separated from shared cortical activity despite partial mutual interference. Tactile stimuli were reliably classified over both regions with and without residual sensation. Importantly, although the stimulation of regions without residual sensation did not evoke tactile perception, it nonetheless elicited measurable cortical responses that supported touch versus no-touch classification. These findings show that a single sensorimotor array can support concurrent motor decoding and tactile detection, and that decodable cortical representations of touch persist across both perceived and non-perceived skin regions. Such signals could be leveraged to enhance motor decoding and to inform sensory-feedback strategies, a step toward bidirectional and embodied neural interfaces after spinal cord injury.

Disclosures: C. Ciucci: None. **L. Pollina:** None. **L. Struber:** None. **A. Carvallo:** None. **S. Chabardès:** None. **T. Aksenova:** None. **G. Charvet:** None. **S. Micera:** None. **S. Shokur:** None. **E. Russo:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.25/FF19

Topic: F.05. Brain-Machine Interface

Support: Blackrock Neurotech/UofU contract no. 10068677

Title: Latent dimensionality influences recovery in manifold-aligned BCI decoder stabilization

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Abstract: Manifold alignment can stabilize brain-computer interface (BCI) decoders after neural recording changes, but this approach requires choosing a latent dimensionality for the neural manifold. Building on Degenhart et al. (2020), who used a 10-dimensional factor analysis (FA) manifold and examined dimensionality effects in supplemental analyses, we tested whether latent dimensionality affects decoder-relevant structure and recovery in offline analyses. We used motor cortical recordings collected by Perich et al. and made publicly available through the DANDI Archive (DANDI:000688), including motor and premotor cortical spiking activity from rhesus macaques performing reaching tasks. Neural activity was binned in 45 ms windows from a 1 s task-aligned analysis window. We fit FA manifolds across latent dimensionalities and evaluated Kalman-filter velocity decoding performance in within-session train/test splits, with additional exploratory analyses of cross-session manifold alignment and controlled spike-count perturbations. Higher latent dimensionalities generally improved FA diagnostics, including shared variance and split-half manifold overlap. Across more than 100 DANDI:000688 sessions, within-session FA/Kalman decoding improved strongly from low-dimensional manifolds and was strongest across moderate-to-high dimensionalities, approaching raw-spike decoding performance. Cross-session alignment reduced loading-matrix discrepancy across consecutive sessions, although decoder transfer remained weaker and more variable than within-session decoding. In pilot perturbation analyses, baseline shifts and combined baseline-shift/dropout conditions produced the clearest decoder failures; manifold-aligned stabilizer updates often improved recovery relative to fixed decoders or unaligned updates, with recovery depending on latent dimensionality. Overall, decoder performance was not fully predicted by monotonic improvements in FA diagnostics. These results suggest that FA model quality alone is insufficient for selecting manifold dimensionality, and that decoder-level performance should be evaluated directly when designing stabilized BCI pipelines.

Disclosures: L. Needham: None. **F. Solzbacher:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Neurotech, Sentiomed, Inc.. F. Consulting Fees (e.g., advisory boards); Blackrock Neurotech.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.26/FF20

Topic: F.05. Brain-Machine Interface

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

Title: Over 20000 hours of in vivo clinical closed-loop DBS recordings reveal asymmetric stimulation-response dynamics in Parkinson's disease

Authors: ***Y. FAN**[1], L. GUAN[1], G. ZHANG[1], H. TIAN[3,1,4], Y. LIU[1,4], Y. WU[1], H. YU[1], L. LI[1,2];
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Abstract: Closed-loop deep brain stimulation (DBS) is an important advance for Parkinson's disease (PD). Beyond using subthalamic nucleus (STN) beta activity to trigger stimulation updates, a central problem is to define how neural activity responds to each stimulation action. This action-response function is the basis for moving closed-loop DBS from threshold triggering to predictable control, yet the STN beta response to stimulation updates has not been formulated as an explicit mathematical relationship using large-scale in vivo clinical data. Here, we used more than 20,000 h of in vivo clinical closed-loop recordings to establish a fast-slow dual-scale model linking stimulation actions to STN beta responses and to reveal asymmetric response functions for stimulation increases and decreases. The dataset included monitored 1-min-resolution recordings and long-term home 10-min sampling recordings. The monitored data contained 2,735 increase and 2,686 decrease events from 15 patients; the home data contained 13,203 increase and 12,904 decrease events from 10 patients. Because beta activity first drives the closed-loop decision and stimulation amplitude is updated afterward, we used first-order causal-lag alignment and defined a direction-corrected response, $R(t)=-\text{sign}(\Delta I)[\beta(t)-\beta(0)]$. Based on this causal order, we modeled the response as an immediate fast component plus a minute-scale slow relaxation component. Event analysis in the monitored 1-min recordings verified this fast-slow structure: the model precisely reconstructed the average event response and outperformed a fixed single-scale structure. It further showed that stimulation increases and decreases had different response trajectories, early amplitudes, and relaxation processes, with the direction-specific fast-slow model outperforming a shared-dynamics model (RMSE: 0.0423 vs 0.0552). Long-term home 10-min data fully reproduced the model-predicted integrated response structure. After projecting the monitored 1-min model to the 10-min scale, real home stimulation events generated direction-corrected responses along the predicted direction, whereas same-patient, same-day no-update background periods did not produce this structure. These results provide the first explicit fast-slow mathematical relationship from stimulation actions to STN beta responses and validate it in monitored and long-term home recordings. Closed-loop DBS is therefore a bidirectional neural interface with causal lag, direction-specific response functions, and dual-scale neural dynamics.

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

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.27/FF21

Topic: F.05. Brain-Machine Interface

Title: Beta and delta outlast high-gamma: frequency-dependent ECoG speech and grasp detection stability over two years in chronic ALS BCI

Authors: *J. WALLNER[1], S. LUO[3], M. ANGRICK[4], D. CANDREA[3], N. E. CRONE[5], D. J. KRUSIENSKI[2];
[2]Biomed. Engin., [1]Virginia Commonwealth Univ., Richmond, VA; [3]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [5]Neurol., [4]The Johns Hopkins Univ., Baltimore, MD

Abstract: Stable long-term decoding remains a critical barrier to clinical deployment of intracranial brain-computer interfaces (BCIs). High-gamma (HG, >70 Hz) activity has been the dominant feature for speech and motor decoders but is susceptible to slow signal drift, and its long-term performance may be further bolstered by incorporating complementary spectral signals. Lower-frequency oscillations carry movement and speech information and tend to be more spatially distributed than HG, raising the question of whether multi-band features can improve longitudinal decoding stability. Chronic electrocorticographic (ECoG) recordings were analyzed from a single participant with progressive amyotrophic lateral sclerosis (ALS) implanted with two 8×8 subdural arrays over the left sensorimotor cortex. The participant performed a syllable-production task and a hand-grasp task multiple times per week over approximately 2.5 years. L1-regularized logistic regression models were trained to detect speech vs. silence and grasp vs. rest using Hilbert-envelope features from canonical frequency bands (delta, theta, alpha, beta, HG), individually and in combination. A sliding-window analysis advanced a 30-session training window through the dataset and evaluated each model on all downstream 10-session test windows, spanning 21 months post-training for speech and 13 months for grasp. Stability was quantified by Theil-Sen slopes and Wilcoxon signed-rank comparisons. HG-only decoders declined steeply for both tasks (speech: −4.3 pp/100d; grasp: −3.4 pp/100d; both $p<0.001$). The HG+beta model for speech showed a practically negligible decline (−0.5 pp/100d; 95.6 ± 0.06% overall), and the HG+beta+delta model for grasp showed no significant decline (+0.00 pp/100d, $p=0.58$; 98.2 ± 0.09% overall). For grasp, delta alone was remarkably stable (+0.5 pp/100d). The multi-band advantage over HG grew over time, reaching +20.6 pp for speech and +10.2 pp for grasp in the final 100 days. Channel importance maps revealed spatially distinct, largely non-overlapping electrode contributions across bands. Incorporating lower-frequency ECoG features substantially improves the longitudinal stability of activity detection without sacrificing accuracy, and may reduce recalibration demands for chronic implantable BCIs while complementing HG-based control.

Disclosures: J. Wallner: None. **S. Luo:** None. **M. Angrick:** None. **D. Candrea:** None. **N.E. Crone:** None. **D.J. Krusienski:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.28/FF22

Topic: F.05. Brain-Machine Interface

Title: ConservedμECoG spatial maps and a shared low-dimensional subspace enable cross-session decoding in non-human primates

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Abstract: Visually guided behaviors arise from distributed neural computations integrating visual inputs with descending motor commands. Brain-machine interfaces (BMI) rely on stable multiregional population representations. Using a high-density μECoG array placed acutely each session over sensorimotor cortex through a chronic recording chamber, we longitudinally mapped cortical activity in non-human primates during visual stimulation, optogenetic stimulation, and center-out reaching. Visually evoked potentials and optogenetic stimulation revealed conserved spatial encoding maps across days, even after deliberate array rotations. During voluntary reaching, high-gamma activity exhibited similarly conserved spatial organization given stereotyped behavioral trajectories.To test whether local field potential stability reflects stable population dynamics, we evaluated cross-session generalization of reach-direction decoding across five sessions. Decoders trained on a single day's high-gamma generalized without retraining: 7-way reach-direction classification retained 89% of within-day performance across days, revealing a transferable signal. To determine whether this signal resides in a stable low-dimensional subspace, we dissociated the effects of dimensionality reduction, behavioral supervision, and state-space dynamics using Preferential Subspace Identification (PSID). Under a matched protocol, we compared a 3-dimensional behavior-supervised PSID latent, supervised static LDA, unsupervised PCA, and the full 214-channel population. The compact PSID latent outperformed full-channel decoding within and across days (PSID/channel ≈1.21) despite ~80× fewer dimensions, whereas matched-dimensional PCA approached chance (PCA/channel ≈0.70) and static LDA only matched the channel ceiling. Thus, behavioral supervision combined with state-space dynamics—not dimensionality reduction alone—recovers a shared low-dimensional neural manifold.These findings demonstrate that sensory inputs and motor outputs in sensorimotor cortex are organized within stable low-dimensional population dynamics and that a behavior-supervised subspace isolates behaviorally relevant neural signals, enabling recalibration-free cross-session decoding. They

highlight μECoG as a robust BMI recording modality capable of capturing distributed neural dynamics that support transferable decoding.

Disclosures: A. Estrada Berlanga: None. **A.L. Orsborn:** None. **J. Viventi:** None. **J. Choi:** None. **B. Pesaran:** None.

Poster

PSTR235: BMI Neurophysiology: Decoding, Neurophysiology and Processing II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR235.29/FF23

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS
NSF NCS DRL
Simons Foundation

Title: Neural basis of overnight motor memory and savings

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Abstract: When we return to a recently learned task, we often begin relearning from a better initial level of performance, a phenomenon known as “savings.” Savings has typically been observed in short-term adaptation to altered sensorimotor mappings. Importantly, savings has also been observed to persist overnight and across multiple days. However, the neural basis of overnight savings remains unclear. Here, we ask whether neural signatures of prior learning in the motor cortex persist across days and facilitate savings during relearning the following day. We address this question with a brain-computer interface (BCI) learning task in a rhesus macaque, where the causal relationship between neural activity in the motor cortex cursor movement is known. To evoke learning, we changed this mapping from an “intuitive” mapping, where the animal could proficiently control the cursor without learning, to a “novel” mapping. Since both mappings are defined by the experimenter, we can evaluate, offline, how appropriate neural activity is for the novel mapping, even when the animal is using the intuitive mapping for cursor control. If post-learning neural activity is more appropriate for the novel mapping than pre-learning activity, it would suggest that the motor cortex stores a memory trace of the novel mapping (Losey et al. 2024). Thus, we ask whether a persistent memory trace could provide the neural basis of overnight savings.
Each session began with a block of intuitive mapping trials. We then introduced a novel mapping (“learning block”) that typically lasted a few hundred trials. Following the learning block, the animal returned to the intuitive mapping (“washout block”). On the following day, the animal was re-exposed to the same novel mapping as on the previous day, allowing us to test whether

the initial performance using the novel mapping on day two was better than on the first exposure. Indeed, we find that initial performance through the novel mapping was better the following day, indicating overnight savings. Furthermore, we observed a memory trace during the first block of intuitive trials on day two. Importantly, we found that the magnitude of overnight savings and the overnight memory trace were correlated for individual targets across sessions.
Overall, these findings suggest that memory traces in the motor cortex can persist across days and may provide a neural mechanism through which prior learning facilitates overnight savings.

Disclosures: T. Arakeri: None. **J. Couras:** None. **E.R. Oby:** None. **A.P. Batista:** None. **B.M. Yu:** None. **S.M. Chase:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.01/FF24

Topic: F.06. Posture and Gait

Support: DOD Grant AL230156

Title: Smartphone-Collected Digital Biomarkers for Motor Performance in Patients with Amyotrophic Lateral Sclerosis (ALS)

Authors: *S. SARAVANAN[1], S. ZEILER[1], R. T. ROEMMICH[1], J. STENUM[1], D. VAIDYA[1], V. ROGALSKI, III[2];
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Abstract: Introduction: Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease affecting both upper and lower motor neurons. The disease has no cure and is uniformly progressive. Nevertheless, ALS is manageable through proper diagnostic action and consistent follow-up. Non-invasive, accessible, smartphone-based digital biomarkers offer an alternative to the current clinical and serum markers, which can be insensitive and/or burdensome. This study evaluated the feasibility of patients with ALS acquiring videos of themselves suitable for upper extremity kinematic analysis.
Methods: Eleven people (n=11) with ALS were recruited from the Johns Hopkins outpatient clinic to record separate videos for finger tapping, hand pronation and supination, and hand opening and closing using a provided smartphone with a custom built application. The application also recorded patient answered ALSFRS-R and ROADS clinical scales. The resulting videos were subsequently pose-estimated using OpenPose, and temporal and amplitude parameters were extracted through MATLAB. Data was successfully extracted from both hands across 3 tasks. The data was then preliminarily compared to current clinic scales to demonstrate correlations.
Results: 10/11 participants were able to record and complete tasks as well as complete clinical

survey questions through the applications, with one participant being unable to successfully record finger tapping, but completing all other tasks. We were able to successfully extract kinematic data for all patient recorded videos, composite the movements into graphical images, and derive the mean, standard deviation, and slopes of both temporal and amplitude parameters of movements for analysis for each subject. A preliminary hypothesis testing comparison with survey data also shows correlations of degeneration, although many did not survive false discovery rate correction due to volume of comparisons.
Conclusions: ALS patients were able to utilize a smartphone application successfully to record movements that yielded tangible kinematic data that can be used for monitoring and comparison. The results are indicative of the potential of smartphone-based kinematic tracking for yielding digital biomarkers of ALS disease state and progression.

Disclosures: S. Saravanan: None. **S. Zeiler:** None. **R.T. Roemmich:** None. **J. Stenum:** None. **D. Vaidya:** None. **V. Rogalski:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.02/FF25

Topic: F.06. Posture and Gait

Title: Long-range SoHo telemetry enables simultaneous physiological monitoring during treadmill exercise in freely moving rats.

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Abstract: Simultaneous behavioral assessment and physiological monitoring in freely moving rodents is challenging. Tethered systems can restrict movement and distort behavior, while short-range telemetry may exhibit low signal quality and artifacts during behavioral tasks. In this study, we evaluated a new implantable telemetry platform (SoHo; Data Sciences International, DSI) that extends transmission range and enables continuous EEG/EMG or ECG, temperature, and activity recording during behavioral tasks. Adult rats (Sprague-Dawley, 463.7 ± 37.4 g) were subcutaneously or intraperitoneally implanted with EEG/EMG or ECG transmitters and recorded during a 2-h home-cage evening baseline. Animals were subjected to an 18-min incremental treadmill (Panlab) exercise protocol with gradually increasing belt speed (from 5 cm/s to 22 cm/s) and synchronous video recording. Relative to home-cage baseline, treadmill exercise produced an increase of 19.4% in cortical theta power (4-8 Hz), of 13.7% in alpha power (8-12 Hz), and of 29.2% in beta power (16-24 Hz). Across ECG-implanted rats, mean heart rate increased from approximately 301 bpm at baseline to 420 bpm during treadmill exercise (39.5%

increase), indicating a cardiovascular response to the incremental workload. Treadmill running was associated with a small rise in subcutaneous temperature of ~1.0 °C and a large increase in locomotor activity counts of roughly 4.3-fold compared with home-cage values. These findings show that SoHo long-range telemetry supports stable acquisition of EEG, ECG, temperature, and activity during controlled treadmill exercise. The platform mitigates the practical constraints of combining behavioral testing with high-quality physiological monitoring in freely moving rodents. Further experiments combining SoHo with other behavioral tests will help validate the system across multiple scenarios.

Disclosures: T. Velie: A. Employment/Salary (full or part-time):; Employee. **J. Van Hee:** A. Employment/Salary (full or part-time):; Employee. **K. Nichols:** A. Employment/Salary (full or part-time):; Employee. **K. Holliday-White:** A. Employment/Salary (full or part-time):; Employee. **J. Alvarez:** A. Employment/Salary (full or part-time):; Employee. **E. Celerier:** A. Employment/Salary (full or part-time):; Employee.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.03/FF26

Topic: F.06. Posture and Gait

Support: JSPS DC1 26KJ1042

Title: Voluntary control of locomotor patterns through a dual-site muscle-spine interface in humans

Authors: *A. OZAKI[1,2,3,4], H. TSUJI[3,4], T. TAZOE[3], Y. NISHIMURA[3];
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Abstract: Human daily life relies on a variety of lower-limb motor behaviors, such as standing, walking, and running. However, individuals with spinal cord injuries (SCI) often lose the ability to voluntarily generate and switch between these movement patterns. Although spinal stimulation to lumber cord can facilitate lower-limb movements, it remains unclear whether distinct locomotor patterns can be voluntarily selected and controlled through spinal circuits. Therefore, this study investigated whether a dual-site muscle-spine interface that allows independent control of stimulation at two spinal sites using muscle activity from the left and right hands enable voluntary control of lower-limb movement patterns and rhythms. 13 healthy participants, 2 participants with chronic complete SCI, and 3 participants with incomplete SCI participated. Ten of 13 healthy participants successfully generated both stepping-like and hopping-like leg movements through the muscle-spine interface and voluntarily switched

between the two patterns. Increasing the rhythm of hand movements significantly increased the cadence of the evoked leg movements, demonstrating voluntary control of locomotor rhythm. Notably, both participants with complete SCI were also able to switch between locomotor patterns. In participants with incomplete SCI, four weekly sessions of muscle-spine interface training were associated with improvements in FTSST and 10MWT performance. These findings demonstrate that a dual-site muscle-spine interface enables voluntary selection, switching, and rhythmic control of distinct locomotor patterns. This approach may provide a novel strategy for restoring voluntary selection and control of lower-limb motor behaviors after SCI.

Disclosures: A. Ozaki: None. **H. Tsuji:** None. **T. Tazoe:** None. **Y. Nishimura:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.04/FF27

Topic: F.06. Posture and Gait

Support: NIH Grant HD-032571
NIH Grant R01NS110550

Title: Unilateral removal of stretch-reflex from major thigh muscles challenges lateral stability, disrupts interlimb coordination, and increases coactivation of antagonists in the cat

Authors: *C. E. HANSON[1], K. OH[4,2], A. N. KLISHKO[1], A. SUBRAMANIAN[2], C. J. GARRETSON[3], W. XU[1], A. FRIGON[5], T. AKAY[6], A. W. ENGLISH[7], R. J. GREGOR[8,1], B. I. PRILUTSKY[9];
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Abstract: Somatosensory feedback during locomotion is integrated within the spinal network to maintain appropriate limb coordination and area of support for balance. Length-dependent feedback from hip flexors and extensors also regulates locomotor cycle phase transitions (Pearson, 2004; Gregor et al., 2006). We hypothesized that compromising this feedback might also affect the number of limbs on the ground, area of support, and locomotor stability. Here, we determined the effects of removing stretch reflexes from major right thigh muscles with self-reinnervation (Cope et al., 1994; Lyle et al., 2016) in 4 adult female cats. We recorded 3D whole body mechanics and EMG activity of right hindlimb muscles during overground walking before and after self-reinnervation of right vastii, rectus femoris, sartorius, biceps femoris anterior and posterior, semimembranosus, and semitendinosus muscles. We found a decrease in stride length

and walking speed, and an increase in step width and stability margins for all limbs following self-reinnervation. The forelimbs were more crouched and the hindlimbs more extended. In addition, vertical ground reaction forces increased for all four limbs. The right hindlimb had reduced lateral and propulsive force, while the contralateral hindlimb and ipsilateral forelimb produced greater propulsive forces. The peaks of extensor joint moments of the right forelimb and hindlimb increased. All self-reinnervated muscles demonstrated at least one new EMG burst in either swing and stance phase, and most muscles had increased EMG activity. As a result, flexors and extensors of the knee and hip were coactivated during both swing and stance phases. This coactivation of knee and hip antagonist muscles was likely responsible for the observed major reduction in knee joint range of motion. The locomotor adaptations of cats with self-reinnervated right thigh muscles closely resembled walking kinematics and coactivation of knee antagonists previously seen in a human patient lacking proprioception (Lajoie et al., 1996). Therefore, we conclude that group Ia afferent input from thigh muscles is critical for maintaining lateral stability, and for proper muscle and interlimb coordination.

Disclosures: C.E. Hanson: None. **K. Oh:** None. **A.N. Klishko:** None. **A. Subramanian:** None. **W. Xu:** None. **A. Frigon:** None. **T. Akay:** None. **A.W. English:** None. **R.J. Gregor:** None. **B.I. Prilutsky:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.05/FF28

Topic: F.06. Posture and Gait

Support: NE Collaboration Initiative No 55423

Title: Tonic cortical engagement scales with balance difficulty and board geometry

Authors: *T. DELIGIANNIS;
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Abstract: Motivation. Standing on an unstable surface demands continuous cortical engagement; yet in mobile-EEG the cortex is usually framed as discrete responses, each locked to a correction. Whether it acts this way, or instead reorganizes its ongoing tonic state as demand rises, is unresolved; whether any such change is scaled by instability geometry is untested. Methods. Quiet standing and wobble-board balance were performed by one healthy adult (IRB approved) at three levels (aspect ratios 0.75/1.0/1.25; Easy/Medium/Hard), on omnidirectional and unidirectional boards. Dry EEG (21 channels, 300 Hz) was recorded with 3D motion capture (100 Hz). The signal was cleaned by artifact-subspace reconstruction (calibrated on standing) and ICA. The primary measure was whole-trial bandpower, normalized to standing, by region. Corrections were taken as board-tilt velocity peaks; spectral change was tested for time-locking,

and post-correction power regressed on peak velocity and excursion (Spearman ρ).
Results. Theta power rose monotonically with difficulty; roughly 100 to 350% above standing was reached by Medium and Hard. Elevation was greatest at central-midline sites, with occipital involvement, on both boards. Greater elevation was produced by the omnidirectional than the unidirectional board, at every level. None was seen for unidirectional Easy; balance demand was tracked, not board contact. By contrast, correction-locked structure was absent; event-locked change was sub-decibel, small against single-trial variability. Post-correction power did not scale with correction magnitude; 2 of 24 region-band cells reached $|\rho| \geq 0.3$, both in the lowest-count condition ($p > 0.05$). The null replicated in a second participant.
Conclusions. As balance demand rises, ongoing cortical activity is reorganized; discrete correction-locked responses are not evoked. This reorganization is scaled by board geometry; the cortex is engaged more by multidirectional than single-axis balance at matched difficulty. Cortical involvement is better read as sustained, geometry-dependent engagement than as responses to single corrections. Signals in mobile-EEG balance work and neurofeedback should be tonic, not event-locked; board geometry is a meaningful axis of challenge.

Disclosures: T. Deligiannis: None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.06/FF29

Topic: F.06. Posture and Gait

Support: FAPESP Grant 2025/02453-0
FAPESP Grant 2024/04054-2
CNPq Grant #311261/2025-6

Title: Two Aspects of Feed-Forward Control During Step Initiation: Task-Specific Early Postural Adjustments and Stabilizing Synergic Organization

Authors: *M. SANTOS DIAS[1], P. B. DE FREITAS, Jr.[2], S. M. FREITAS[3], M. L. LATASH[4]; [1]Cruzeiro do Sul Univ., São Paulo, Brazil; [2]Inst. de Ciencias da Atividade Fisica e Esporte, Cruzeiro Do Sul Univ., São Paulo, Brazil; [3]Cidade De Sao Paulo Univ., São Paulo, Brazil; [4]Dept. of Kinesiology, Penn State Univ., University Park, PA

Abstract: Step initiation requires feedforward processes that prepare the body for an upcoming action while preserving the stability of relevant performance variables. Early postural adjustments (EPAs) modify the mechanical state of the body prior to movement, whereas within the Uncontrolled Manifold (UCM) framework, anticipatory synergy adjustments (ASAs) transiently reduce the stability of task-specific variables in preparation for their intended change. We tested whether these mechanisms adapt similarly to changes in the mechanical demands of

an upcoming step. Sixteen healthy young adults performed quiet standing, voluntary body sway, and self-initiated stepping tasks under three surface-height conditions (step-up, level, and step-down). EMG activity from 16 trunk and lower-limb muscles and center of pressure (COP) coordinates were recorded. Principal component analysis (PCA) identified four M-modes in the muscle activation space, which served as elemental variables within the UCM framework. Jacobian matrices relating changes in M-modes to COP displacements were used to quantify synergies and their anticipatory changes. Synergies stabilizing COP in the anteroposterior (AP) direction were present during steady-state standing across all conditions, whereas synergies stabilizing COP in the mediolateral (ML) direction were absent. Importantly, neither the synergy index nor ASA magnitude differed significantly across task conditions, and ASAs were not detected for either direction. In contrast, EPAs showed task-dependent adaptations. Step-down was associated with earlier EPA onset and larger COP displacements than step-up for both AP and ML directions ($p < 0.01$). These findings support a distinction between two aspects of feedforward control during step initiation: the stability of COP-related performance variables remained largely invariant across task conditions, whereas EPAs showed task-specific modulation consistent with the anticipated mechanics of the forthcoming action. The results suggest that preparation for stepping relies primarily on adjustments to body mechanics rather than on changes in the stability of task-level performance variables, thus supporting the view that EPAs and synergies represent distinct components of motor preparation.

Disclosures: M. Santos Dias: None. **P.B. de Freitas:** None. **S.M. Freitas:** None. **M.L. Latash:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.07/Web Only

Topic: F.06. Posture and Gait

Title: Effects of limiting center of pressure displacement on anticipatory postural control and attentional allocation during unilateral arm abduction

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Abstract: Rapid arm movements while standing result in automatic activation of the postural muscles of the legs and trunk before activation of the focal muscles of the arms (Belen'kii et al., 1967). A more forward-leaning posture before bilateral arm flexion is reportedly associated with earlier onset of postural muscle activity (Benvenuti et al., 1997). We have reported that a similar situation can be created using an inclination board, which is inclined when the center of pressure (CoP) exceeds a certain range (Fujiwara and Yaguchi, 2013). The sensory information from

plantar pressure and some postural muscles while maintaining the standing posture before arm movement are different in the former case, but the same in the latter case. The latter setting is thus considered better for examining the influence of the difficulty of the postural control task itself. When task difficulty during arm movement is high, attention would be directed to the task, and/or postural preparation would occur. Aspects of attention and motor preparation can reportedly be investigated using the contingent negative variation (CNV) of event-related brain potentials (Walter et al., 1964). The purpose of this study was to examine changes in attentional allocation and postural muscle activities when the postural control task with unilateral arm abduction becomes more difficult without changing the posture before the movement, using CNV and the limitation of CoP range toward arm movement direction. In response to a second visual signal (S2) presented 2 s after a warning signal, 16 healthy adults abducted the right arm at maximum speed. Arm abduction trials were repeated 30 times under no-limitation (nLC) and limitation (LC) conditions. The 70% rightward range of CoP displacement caused by arm abduction was calculated under nLC, and the floor inclined by the weight of the subject when CoP extended beyond that range in LC. Subjects were instructed to not incline the floor during arm abduction. CoP displacement by arm abduction, onset time of postural muscles with respect to middle deltoid, and CNV mean amplitude for 100 ms just before S2 were analyzed. Under LC, compared with nLC, the following significant changes were found: smaller CoP displacement; earlier onset times of postural muscles; and larger CNV amplitude. Onset times of postural muscles were significantly and negatively correlated with CNV amplitude. By limiting the rightward range of CoP displacement, a strategy that significantly reduced the disturbance associated with arm movement would be adopted. In this case, more attention would be paid to the motor preparation and/or S2, resulting in early onset of postural muscle activities.

Disclosures: C. Yaguchi: None. **K. Fujiwara:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.08/Web Only

Topic: F.06. Posture and Gait

Support: JSPS KAKENHI 19K11589

Title: The effect of postural demands associated with weight loads on the development of anticipatory postural muscle activation during bilateral arm flexion

Authors: *T. KIYOTA[1], K. FUJIWARA[1], T. NAKAMURA[2], M. IREI[3], A. NAKAMURA[4]; [1]Kanazawa Gakuin Univ., Kanazawa, Japan; [2]Osaka Child Welfare Col., Osaka-shi / Osaka, Japan; [3]Osaka Hlth. Sci. Univ., Osaka, Japan; [4]Osaka health and science university, Osaka-Shi, Japan

Abstract: We investigated the effect of postural demands associated with weight loads on the development of activation timing of postural muscles during bilateral arm flexion.The study participants consisted of 10 adults and 10 children aged 4-6. In response to a visual stimulus, participants flexed both arms from a fully extended position as quickly as possible, stopped their arms horizontally at the shoulder level, and maintained that position for 2 s. Fifteen test trials were performed for each condition. For the postural conditions, the control condition (CTR) involved performing the task under no-load conditions, in a resting standing position. For the weighted load conditions, adults performed the task with loads of 1%, 3%, and 5% of their total body weight applied to both wrists, while young children performed the task with a load of 1% of their body weight. By using surface electromyography, the duration from the burst onset of the postural muscles to that of the anterior deltoid [AD] was measured as the starting time of the postural muscles (rectus abdominis [RA], erector spinae [ES], rectus femoris [RF], biceps femoris [BF], tibialis anterior [TA], gastrocnemius medialis [GcM], and soleus [SOL]). The starting time was presented as a negative value when the burst onset of the postural muscles preceded that of AD, which was defined as the preceding activation. A positive value for the starting time was defined as delayed activation.In adults, the burst onsets of ES and BF in all conditions significantly preceded that of AD. No significant effects of load weight were observed in ES. In contrast, for BF, the onset of activation was significantly earlier at 1% and 3% compared to the CTR condition, with the 3% condition showing the earliest onset. However, under the 5% condition, no significant difference was observed relative to the CTR condition. In young children, the burst onset of ES significantly preceded that of AD in both conditions, whereas no preceding activation was observed in BF under any condition. A significant difference in the onset of ES activity was observed between the CTR and 1% conditions, but no such difference was observed for the BF. In conclusion, to adapt to weight loads, adults show coordinated preceding activation of both the trunk (ES) and lower limb (BF) muscles. In contrast, young children exhibit an inability to coordinate these muscles, relying only on the earlier activation of the trunk muscles.

Disclosures: T. Kiyota: None. **K. Fujiwara:** None. **T. Nakamura:** None. **M. Irei:** None. **A. Nakamura:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.09/Web Only

Topic: F.06. Posture and Gait

Title: Postural control adaptability during sinusoidal floor oscillation in the anteroposterior and mediolateral directions

Authors: *K. FUJIWARA, N. KIYOTA, T. KIYOTA;
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Abstract: The human standing posture is characterized by a stratified physical structure. Bernstein proposed that one of the fundamental problems in human motor control is the high number of degrees of freedom in the body to be controlled. Postural control in the anteroposterior (AP) direction is considered to involve more degrees of freedom than in the mediolateral (ML) direction, thereby requiring more complex regulatory mechanisms. We investigated postural control adaptability in an upright stance with eyes closed while a force platform was oscillated sinusoidally in the AP and ML directions. Subjects were 29 healthy male university students divided into two groups: 15 for ML oscillation and 14 for AP oscillation. There were no significant differences between the groups in age, height, weight, and foot length. Subjects repeated at least five trials of a task in which they maintained a standing posture for 60 seconds on the force platform oscillating sinusoidally with an amplitude of 2.5 cm and a frequency of 0.5 Hz, until reaching a plateau. Using the force platform and a position sensor system, we measured the fluctuation of the center of pressure (CoP) and the body sway of the pelvis and vertebra prominens (C7). The mean speed of CoP fluctuation (CoP speed) was calculated using the weighted 5-point moving average method. To investigate the frequency components mainly involved in body sway, fast Fourier transformation analysis was performed on each waveform, and the spectrum amplitudes at 0.5 Hz were measured. Furthermore, to examine the similarity and phase lag relative to the floor oscillation, cross-correlation analyses of the body sway waveforms were performed.CoP speed decreased significantly up to the third trial in the ML direction and the fourth trial in the AP direction, reaching a plateau thereafter. As postural control adaptation progressed, the spectrum amplitude of body sway decreased more significantly in higher body parts. The attenuation rate was greater in the ML direction than in the AP direction. Body sway in higher body parts showed a significant phase lag relative to the floor oscillation in both directions. This phase difference between the pelvis and C7 decreased particularly during ML oscillation.

Disclosures: K. Fujiwara: None. **N. Kiyota:** None. **T. Kiyota:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.10/FF31

Topic: F.06. Posture and Gait

Support: Swiss National Science Foundation grant 22922

Title: Neuromuscular characterization of gait in Parkinson's disease patients with Freezing of Gait

Authors: *M. LASFARGUES[1,3], E. VARIOLA[4], D. LEAL PINHEIRO[4], V. MENDEZ[4], N. CONCEIÇÃO[5,6], A. C. DONATI[7,8], D. COELHO[9], S. MICERA[4,10], S. SHOKUR[4,10], M. BOURI[2];

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Abstract: Freezing of Gait (FoG) is characterised by a paroxysmal inability to step effectively despite intention, it affects up to 80% of advanced Parkinson's disease (PD) patients (Gilat et al., 2026) and represents a leading cause of falls, hospitalization, and social isolation (Faerman et al., 2025). Despite its clinical impact, the neuromuscular mechanisms underlying FoG remain incompletely understood.This study uses intermuscular coherence (IMC); reflecting shared neural drive between muscles via corticospinal pathways; to characterise muscle coordination in PD patients with and without FoG. Ten PD patients (five with confirmed FoG, five without) performed three gait tasks designed to elicit freezing: eight-shape circuit, narrow corridor navigation, and obstacle crossing (10 repetitions: 5 single-task and 5 dual-task). Surface EMG was recorded bilaterally from four lower-limb muscles: tibialis anterior (TA), gastrocnemius medialis (GM), biceps femoris (BF), and rectus femoris (RF), yielding 12 ipsilateral muscle pairs. IMC was computed via continuous wavelet with cross-spectral Gaussian smoothing across three frequency bands: alpha (8-13 Hz), low beta (13-21 Hz), and high beta (21-35 Hz). Preliminary analysis comparing freezing episodes to non-FoG periods across the five FoG patients shows consistently higher IMC scores across all frequency bands and muscle pairs, suggesting a global increase in common neural drive during freezing. The largest effects were observed in the alpha band, with all ipsilateral pairs showing markedly higher IMC, affecting both agonist pairs: GM-BF ($\Delta \approx +0.20$) and GM-RF ($\Delta \approx +0.22$), and antagonist pairs: TA-RF ($\Delta \approx +0.15$) and TA-GM ($\Delta \approx +0.16$). A similar but weaker pattern was observed in the low beta band (mean $\Delta \approx +0.03$). It is consistent with reported TA-GM co-contraction during FoG (Breu et al., 2021). At the group level (FoG vs non-FoG), no significant differences were found, likely due to limited statistical power and high inter-individual variability. Yet alpha and beta-band trends emerged: FoG patients showed reduced TA-BF coherence (alpha: -0.040, low beta: -0.028, high beta: -0.019), while non-FoG patients exhibited higher GM-BF coherence ($+0.029$, $+0.030$, $+0.022$). As TA-BF are synergistic during swing, unlike GM-BF, their reduced coupling in FoG patients suggests disrupted coordination, consistent with abnormal locomotor timing in freezers and a broader gait deficit. These preliminary findings support IMC as a potential marker of altered neuromuscular dysfunction during freezing of gait and suggest that IMC may constitute a neurophysiological signature differentiating freezers from non-freezers.

Disclosures: M. Lasfargues: None. **E. Variola:** None. **D. Leal Pinheiro:** None. **V. Mendez:** None. **N. Conceição:** None. **A.C. Donati:** None. **D. Coelho:** None. **S. Micera:** None. **S. Shokur:** None. **M. Bouri:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.11/FF32

Topic: F.06. Posture and Gait

Support: NIH grant NS110550
CIHR grant 162357
CIHR grant 565931

Title: Step-by-step control of lateral stability during walking in wild type and Egr3-KO mice

Authors: *A. N. KLISHKO[1], C. HANSON[1], K. G. MACKINNON[2], B. I. PRILUTSKY[1], T. AKAY[2];
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Abstract: Inherent mechanical stability of walking mice due to their relatively wider step width and crouched posture (Akay et al., 2026) might reduce the role of somatosensory motion-dependent feedback in control of lateral stability. This could diminish the translational value of the mouse model system for understanding somatosensory deficits in humans. To examine the role of group Ia/II muscle spindle afferents in control of lateral stability in the mouse, we compared locomotor kinematics and measures of lateral stability between 5 wild type (WT) mice and 5 Egr3-KO mice lacking functional muscle spindles. We recorded (500 Hz sampling rate) and analyzed kinematics of hindlimb/forelimb paws and the body center of mass (CoM) in the horizontal plane and right hindlimb in the sagittal plane during walking on a treadmill with speed of 0.1 m/s. General kinematic characteristics of walking cycles did not differ between the WT and Egr3-KO groups: cycle time (WT: 0.425±0.040 s vs. KO: 0.400±0.063 s, $p = 0.192$), duty factor (0.589±0.035 vs. 0.599±0.054, $p = 0.923$), and hindlimb step length (23.1±4.4 mm vs. 24.6±5.1 mm, $p = 0.652$). On the other hand, lateral stability measures differed significantly. The lateral dynamic stability margin (8.3±1.4 vs. 5.6±1.2 mm, $p = 0.003$), hindlimb step width (25.9±2.9 mm vs. 16.5±2.9 mm, $p < 0.001$), lateral range of CoM motion (4.3±1.5 mm vs. 2.9±1.3 mm), and minimum hip height in stance (22.4±2.8 mm vs. 17.4±3.5 mm, $p = 0.045$) were smaller in the Egr3-KO than in the WT group. The Egr3-KO mice had greater crouching (the ratio of hip minimum height in stance over the anatomical hindlimb length: 0.486±0.045 vs. 0.410±0.058, $p = 0.043$) and flexion in ankle (55.9±11.1 deg vs. 34.3±11.4 deg, $p < 0.001$) and knee (90.3±8.2 deg vs. 77.8±8.6 deg, $p = 0.003$) joints at paw contact than the WT mice. We also found that both groups of mice controlled lateral stability on a step-by-step basis. The correlation coefficients between lateral deviations in CoM motion from the midline and the subsequent deviations of the lateral borders of support from their mean values were $r = 0.616$, $p < 0.001$ and $r = 0.540$, $p <0.001$ for the WT and Egr3-KO mice, respectively. Since the lack of group Ia/II spindle afferents caused extreme locomotor adaptations that enhances stability (lowering body so that the stomach fur was nearly touching the ground), we concluded that despite the inherent mechanical stability of the mouse, muscle length-dependent sensory feedback is important for lateral stability of walking mice. Load- and touch-dependent Golgi-tendon organ and cutaneous

afferents are intact in the Egr3-KO mice and appear to contribute to step-by-step regulation of lateral balance.

Disclosures: A.N. Klishko: None. **C. Hanson:** None. **K.G. MacKinnon:** None. **B.I. Prilutsky:** None. **T. Akay:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.12/GG1

Topic: F.06. Posture and Gait

Support: NIH Grant 1R01NS124814

Title: Characterizing dynamic postural instability and motor adaptation profiles during perturbed treadmill walking

Authors: L. WINTER, M. VACA, B. LYU, J. TORBENSON, R. RAJAMANI, ***S. E. COOPER**;
Univ. of Minnesota, Minneapolis, MN

Abstract: Clinical gait assessments typically use unperturbed walking or static tests, omitting dynamic stability under unexpected perturbations. This leaves a critical gap: we currently lack a standardized framework to quantify how the central nervous system adapts to dynamic balance threats, limiting our ability to identify specific motor learning deficits or optimize interventions like deep brain stimulation in Parkinson's disease. To address this, our study established a multi-sensor profile of dynamic locomotor adaptation to determine whether healthy adults exhibit predictable recovery mechanics. To date, 22 healthy participants completed a protocol on a treadmill featuring automated belt acceleration and deceleration perturbations delivered every ~8 s during the right or left swing phase. Swing leg assignment and perturbation direction were randomized. Center of pressure (COP) data from a validation subset (n=12) were analyzed across 1,700 unique perturbation events to validate the analytical pipeline before replicating on the remaining dataset. Lower-body kinematics from 5 inertial units and plantar pressure via instrumented insoles were concurrently recorded.
Postural instability was quantified by mapping mediolateral COP displacement and velocity into a 2D phase space, using localized polar phase angles to identify perturbation timing within the gait cycle. The peak deviation of this perturbed trajectory from the unperturbed, steady-state cycle defined the maximum instability score (SI_Max). Experimental trials revealed a significant but negligible difference between perturbation types ($p=0.0017$; Cohen's $d=-0.181$), indicating no systematic impact of acceleration vs. deceleration perturbation. Reactive balance recovery did not differ by swing leg onset ($p=0.3565$, Cohen's $d=0.095$), demonstrating symmetry in these young healthy adults. Paired analysis between naive (first 5) and adapted (last 5) perturbations

revealed a significant session-wide reduction in peak instability of 2.109 arbitrary units ($p=0.0191$, Cohen's $d=0.792$). Linear mixed-effects modeling showed that log-transformed trial progression predicted error reduction (Slope=-0.433, $p<0.001$).
These findings demonstrate that automated perturbations drive a predictable adaptation process characterized by a rapid, logarithmic decay in state-space displacement. By defining these normative kinetic and kinematic properties, this study establishes the physiological baseline required to detect abnormal motor learning, lateral asymmetry, and compensatory mechanics in clinical cohorts prone to falls.

Disclosures: L. Winter: None. **M. Vaca:** None. **B. Lyu:** None. **J. Torbenson:** None. **R. Rajamani:** None. **S.E. Cooper:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.13/GG2

Topic: F.06. Posture and Gait

Support: FAPESP

Title: Acute effects of unilateral ankle loading on spatial and temporal gait symmetry in overground walking

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Abstract: Locomotor adaptation paradigms have been widely used to investigate walking control. However, before unilateral mechanical loading can be considered for overground adaptation protocols, it is necessary to determine how short exposure to different load magnitudes affects gait symmetry. Therefore, the purpose of this study was to investigate the effects of two unilateral mechanical loading magnitudes on spatial and temporal gait symmetry in non-disabled adults. Thirty-two adults with no known gait impairment walked at a self-selected speed over an electronic walkway. Two experimental blocks were performed in randomized order, differing only in the magnitude of the unilateral mechanical load applied at the ankle (3% or 5% of body weight). Each block consisted of four conditions: baseline walking without a cuff (BL1), walking with an unloaded cuff (BL2), walking with the unilateral load (L3 or L5), and post-load walking without the cuff or load (PL3 or PL5). Participants completed 5 BL1 trials, 5 BL2 trials, 10 loaded trials, and 10 post-load trials in each experimental block. Data from baseline conditions were averaged across all trials, whereas data from loaded and post-load conditions were analyzed separately for the first and last five strides. The presence of the cuff alone increased swing duration asymmetry but did not affect step length symmetry. Changes in

step length symmetry emerged during the final loaded strides, exhibited an aftereffect following load removal, and returned toward baseline values by the end of the post-load condition. Swing duration symmetry was altered during loaded walking, with greater asymmetry observed with the 5% than the 3% load. Following load removal, swing duration also exhibited an aftereffect and returned toward baseline values by the end of the post-load condition. These preliminary findings indicate that unilateral ankle loading affects spatial and temporal gait symmetry differently during short bouts of overground walking. Whereas spatial asymmetry emerged later during loaded walking, temporal asymmetry was immediately affected and was sensitive to load magnitude. Because exposure to loading consisted of only 10 trials over a short walkway, these findings should be interpreted as acute responses to mechanical loading rather than evidence of locomotor adaptation.

Disclosures: A.M. Barela: None. **A.S. Lima:** None. **D.S. Reisman:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.14/GG3

Topic: F.06. Posture and Gait

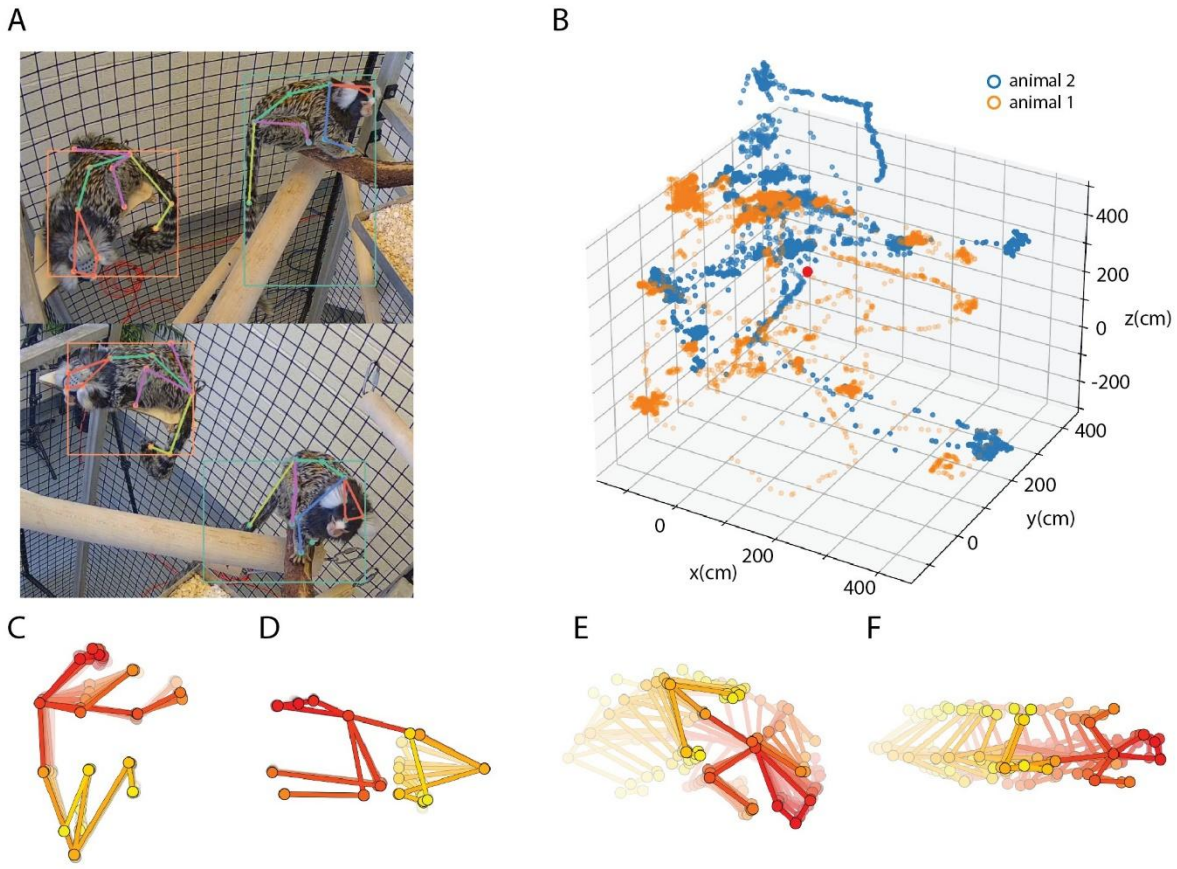
Support: NIH Grant 1RF1NS132033-01

Title: Three-dimensional pose estimation and behavior segmentation of in-cage, spontaneous behavior for pair-housed marmosets

Authors: *J. LEE, N. G. HATSOPOULOS;
Univ. of Chicago, Chicago, IL

Abstract: Marmosets are highly social animals that show a wide repertoire of behaviors in their natural habitat, and there is a strong interest in automatically tracking these behaviors in their housing cages. There are many varieties of automated pose tracking systems such as DeepLabCut, SLEAP, Anipose, including those that were developed specifically for non-human primates. However, such systems fail when objects mimicking their natural habitat are included inside their cage. To overcome these problems, we decided to use a combination of MarmoPose, a deep-learning-based 3D pose-tracking system designed for tracking multiple common marmosets with minimal hardware requirements, and Keypoint-Moseq, a machine learning-based platform for parsing continuous keypoint data into discrete actions.
We first annotated for each camera 16 locations of the body (A) (head, left/right ear, neck, spinemid, left/right elbow/hand/knee/foot, tailbase, tailmid and tailend) to train a detection model to detect the bounding box of each animal, followed by a pose estimation model to predict the 16 body locations described above. Then, MarmoPose estimated the 3D poses of each animal through triangulation of the predicted body locations. Using this triangulated 3D pose data, we

then identified behavior syllables (C-F) across time using Keypoint-Moseq allowing us to accurately estimate both animals' location, velocity and behavior (B). This also allowed us to quantify the kinematics of the same body parts across different behavior categories. Combined with our wireless recording techniques, this provides a powerful tool to further study the neural correlates of natural, spontaneous behavior in freely moving marmosets.



Disclosures: J. Lee: None. **N.G. Hatsopoulos:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.15/GG4

Topic: F.06. Posture and Gait

Support: NIDILRR

Title: Asymmetric Prefrontal High-Gamma Connectivity During Proprioception-Dependent Stepping Following Anterior Cruciate Ligament Reconstruction: A Pilot EEG Study

Authors: *S. LEE[1], P. FU[2], L.-Q. ZHANG[3];
[1]Univ. of Maryalnd Baltimore, Baltimore, MD; [2]Univ. of Maryalnd Baltimore, College Park, MD; [3]PTRS, Orthopaedics, Bioengineering, Univ. of Maryland, Baltimore, MD

Abstract: Proprioceptive deficits following ACL reconstruction are well-documented behaviorally, yet the cortical mechanisms by which impaired joint afference disrupts executive sensorimotor integration remain unknown. We applied a robotic off-axis elliptical stepping paradigm to examine high-gamma directed EEG connectivity in two individuals following unilateral ACL reconstruction (left and right surgery, respectively; ~9 month). Participants performed foot pivoting on the elliptical trainer under a no-visual-feedback free mode, in which transverse friction was removed to simulate walking on ice, allowing unconstrained pivoting. Without visual feedback, proprioception becomes the primary sensory input for motor control. High-density EEG (128 channels) was source-reconstructed to 14 cortical regions including frontal eye fields (FEF), dorsolateral prefrontal cortex (DL-PFC), primary motor (MC) and somatosensory (S1) cortices, superior parietal lobule (SPL), temporo-parietal junction (TPJ), and visual cortex. Directed connectivity in the high-gamma band (60-90 Hz) was estimated using Phase Transfer Entropy (PTE), and net outflow and inflow were derived for DL-PFC.R. Pearson correlations between regional PTE and root-mean-square pivot angle (RMSAngle) were computed per limb. On the operated limb, DL-PFC.R outflow exceeded inflow (7.96 vs 5.04 PTE units), while the intact limb showed the reverse (6.96 vs 6.04). Inflow to DL-PFC.R from 11 of 13 regions correlated positively with RMSAngle on the intact limb ($r = 0.24$-0.50), including FEF ($r = 0.29$-0.50), MC ($r = 0.29$-0.49), and TPJ ($r = 0.33$-0.43) (**Figure 1**). This network-wide convergence was absent on the operated limb, indicating that executive cortex is decoupled from the sensorimotor network during operated-limb control. These findings suggest that disrupted high-gamma routing from the dorsal attention network and sensorimotor cortices to DL-PFC.R represents a specific cortical mechanism of ACL-related proprioceptive impairment and a candidate biomarker for sensorimotor recalibration in rehabilitation.

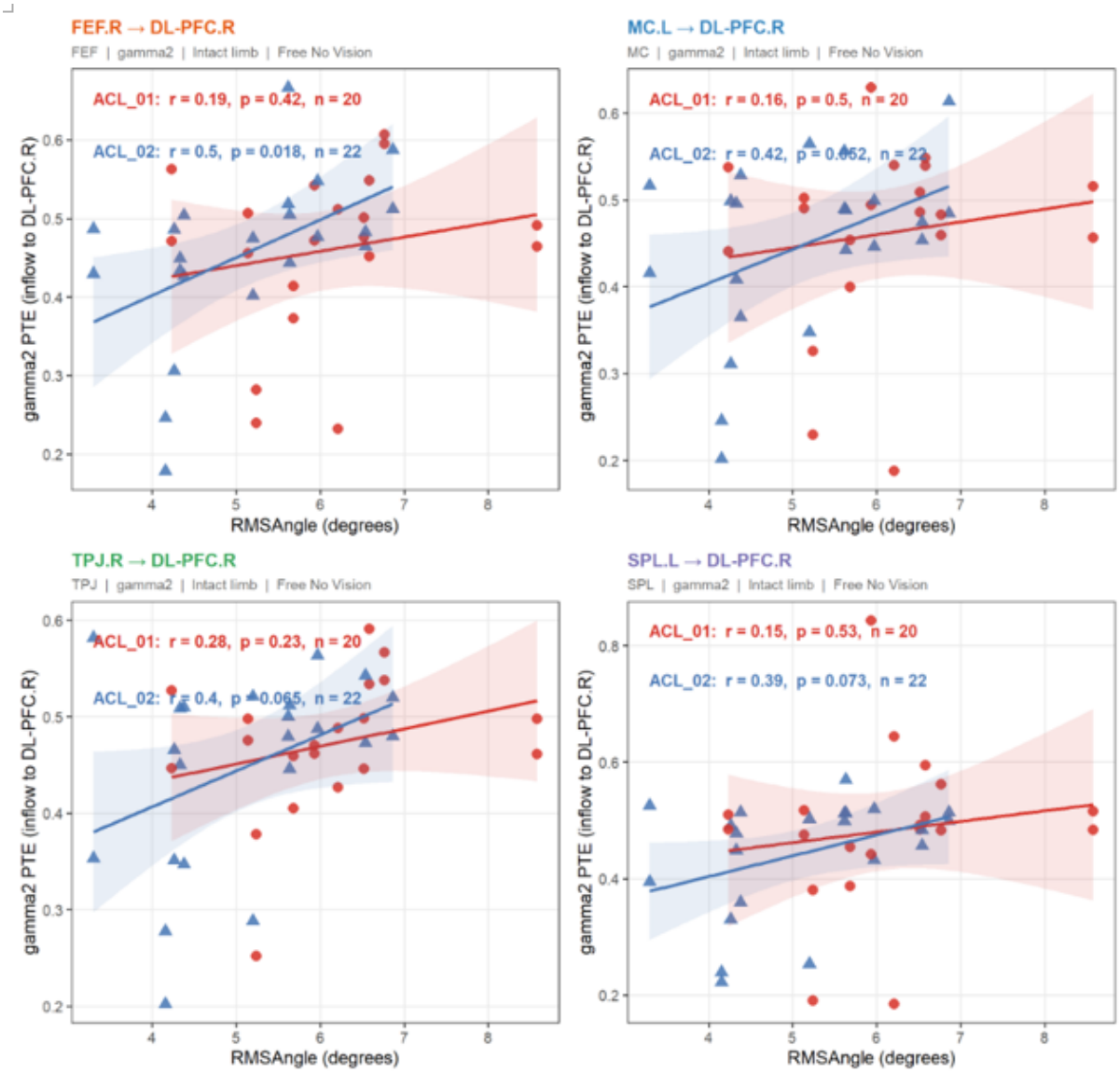


Figure 1. High-gamma directed connectivity from sensorimotor and frontoparietal regions to right dorsolateral prefrontal cortex (DL-PFC.R) scales with pivot angle on the intact limb during proprioception-dependent stepping.

Disclosures: S. Lee: None. **P. Fu:** None. **L. Zhang:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.16/GG5

Topic: F.06. Posture and Gait

Support: NIH 1R01AG089175-01
Pittsburgh Pepper Center P30AG024827
NIH R90DA060340-02S1
NIH K23AG076663

Title: Decreased ability to suppress feedback response to perturbation contributes to reduced locomotor savings with aging

Authors: *S. LIU[1], A. M. WEINSTEIN[2], G. TORRES-OVIEDO[3];
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Abstract: Locomotor savings, the ability to recall learned movements when re-encountering a familiar environment, is essential for community ambulation. Older adults exhibit lower locomotor savings than younger adults, but the neuromuscular mechanisms remain unknown. To address this gap, we used a novel method to identify electromyography (EMG) features reflecting neuromuscular feedback and feedforward control during walking and quantified age-related differences in these controls. We hypothesized that locomotor savings manifest as attenuated feedback responses (reflecting environmental familiarity) and enhanced feedforward responses (reflecting faster retrieval of context-specific walking patterns), with both effects more pronounced in younger adults. To test this, 21 older (71.85 ± 3.14 years old, 11 female) and 21 sex-matched younger (25.05 ± 5.20 years) adults completed three days of split-belt treadmill walking, an established locomotor savings paradigm where one leg moves faster than the other. Bilateral surface EMG was recorded from 20 leg muscles and decomposed into feedback (measured by naïve activity during early split-belt exposure) and feedforward (measured by expert activity following three days of practice) components. Two-way mixed ANOVAs assessed the age-by-session (pre- vs. post-practice) effects on each component. We found that younger adults showed greater practice-induced attenuations in feedback responses in fast-leg distal muscles than older adults (significant interaction in medial gastrocnemius: adjusted $p = 0.045$ with large $\eta_p^2 = 0.23$; peroneus: adjusted $p = 0.0498$ with large $\eta_p^2 = 0.21$), while changes in feedforward responses did not differ between groups (no interaction). Across both groups, feedback responses decreased across all muscles (session main effect: pooled $\eta_p^2 = -0.29$), but feedforward responses increased only in fast-leg distal muscles (pooled $\eta_p^2 = 0.04$). The results suggest that both age groups achieved savings by attenuating reactive feedback to the split-belt perturbation and expediting the retrieval of previously learned feedforward patterns, but younger adults suppressed reactive feedback more effectively. In sum, while older adults retain the capacity to form and retrieve context-specific motor patterns, they exhibit a diminished ability to rapidly downregulate reactive responses, suggesting mobility rehabilitation for older adults should target reactive feedback mechanisms.

Disclosures: S. Liu: None. **A.M. Weinstein:** None. **G. Torres-Oviedo:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.17/GG6

Topic: F.06. Posture and Gait

Title: Electromyography-based upper limb machine learning assessment for essential tremor

Authors: *B. D. TONDRE[1], A. BURGESS[2], A. GUNDUZ[3];
[1]Univ. of Florida, TAMPA, FL; [3]Biomed. Engin., [2]Univ. of Florida, Gainesville, FL

Abstract: Essential tremor (ET) is a common movement disorder, affecting over 7 million people in the United States. ET is characterized by involuntary tremor (~4-12 Hz) during purposeful movement primarily within the upper limbs. About half of ET patients are medication-refractory, hence deep-brain stimulation (DBS) is a well-established, FDA-approved therapy for treatment. DBS targeting the ventral intermediate nucleus of the thalamus (VIM) is beneficial for suppressing tremors. However, continuous high-frequency stimulation can cause off-target side effects, which can hinder motor performance. Currently, there are no objective or standardized measures within clinical settings to identify upper tremor. We hypothesize that upper limb tremor activity can be accurately classified and predicted based on muscle activity captured by electromyography (EMG). The objective of this research is to evaluate the performance of machine learning approaches in classifying upper limb tremor activity. Five ET DBS (4-unilateral, 1-bilateral) implanted with the Medtronic Summit RC+S system were recruited to evaluate DBS performance across 24 months. Tremor severity was independently evaluated by a blinded neurologist using the Fahn-Tolosa-Marin Tremor Rating Scale. Participants performed several behavioral tasks to elicit tremors with and without stimulation while wearing wearable sensors that capture EMG and accelerometry (ACC). Supervised machine learning (ML) approaches (i.e. random forest (RF), support vector machine (SVM), recurrent neural network (RNN), convolutional neural network (CNN), etc.) were developed from extracting time, frequency, and amplitude features. Models were evaluated using five-fold cross-validation and performance metrics including accuracy, precision, sensitivity, specificity, F1-score, and confusion-matrix-derived false-positive and false-negative rates. The results of this work demonstrate that EMG-based ML approaches can accurately characterize and quantify tremor activity based on stimulation conditions. The effectiveness of ML approaches was evaluated offline with a target classification accuracy of 95%. CNN was superior in extracting spatial features from EMG signals when compared to SVM and RF. However, RF can capture nonlinear relationships, which is beneficial in smaller datasets. These preliminary findings support further evaluation of wearable-sensor-based classification as a tool for identifying and classifying upper limb tremor. Ultimately, this work seeks to be used as a foundation to distinguish upper limb and lower limb tremor to identify off-target lower limb tremor within clinical settings.

Disclosures: B.D. Tondre: None. **A. Burgess:** None. **A. Gunduz:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.18/GG7

Topic: F.06. Posture and Gait

Support: NIH Grant P41 EB018783 (Wolpaw)
NYS Spinal Cord Injury Research Board C38338GG (Wolpaw),
VA SPiRE NCT05880251 (Brangaccio)
Stratton VA Medical Center

Title: Operant Up-Conditioning of the Human Soleus Spinal Stretch Reflex During Stretch-Shortening Cycle Movement: Methods Development and Initial Results

Authors: J. HOWALDT[1], **J. A. BRANGACCIO**[2], L. RUGGIERO, Sr.[3], A. K. CHETOUANI[4], J. HILL[2], J. S. CARP[2], *T. M. VAUGHAN[5], J. R. WOLPAW[2], M. GRUBER[1];
[1]Human Performance Res. Centre, Dept. of Sport Sci., Univ. of Konstanz, Konstanz, Germany; [2]Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr., Albany, NY; [3]Biomed. Sci., Univ. of Padua, Padua, Italy; [4]Ctr. for Sport Sci. and Univ. Sport, Univ. of Vienna, Vienna, Austria; Neuromuscular Res. Center, Univ. of Jyväskylä, Jyväskylä, Finland, Vienna, Austria; [5]Stratton VA Med. Ctr., Albany, NY

Abstract: Human locomotion relies on the stretch-shortening cycle (SSC), in which elastic energy is stored and then used to enhance mechanical efficiency in the muscle-tendon unit. The Ia-afferent pathway, which produces the monosynaptic spinal stretch reflex (SSR), contributes to rapid regulation of muscle stiffness during SSC movements. Wolpaw, Thompson, and their colleagues showed that the SSR and its electrical analog the H-reflex can be operantly up- or down-conditioned in humans and animals, and that appropriate conditioning can enhance recovery of locomotion in people with spinal cord injury or other disorders (for review: doi:10.3389/fnint.2014.00025). We are now exploring the possibility that soleus SSR up-conditioning can enhance performance of a high-velocity SSC task (hopping) in healthy people. In a pilot study, a healthy adult completed 5 sessions of bilateral hopping, one session/week for 5 weeks. Hopping was performed at 2.2 Hz; each hop was as explosive as possible. Right soleus electromyographic (EMG) activity was recorded from the skin. SSR size was measured as the amplitude of mean rectified EMG activity 35-65 ms after ground contact. Each session had 7 sets of 30 hops separated by 3-min rest periods. The first set was a control set in which no feedback as to SSR size was given. In the next 6 sets, each hop was followed by immediate visual feedback indicating whether SSR size was above or below a 66% criterion derived from the previous set's performance distribution. If it was above the criterion, the hop was a success; if it was below, the hop was not a success. In subsequent analyses, SSRs were stratified by matched preceding EMG activity and preceding flight time using binning to standardize comparisons across levels of background EMG activity and mechanical state. We found a nonlinear increase in soleus SSR size, with an 8% increase from session 1 to session 5. This change was accompanied by a 5% increase in reactive strength index, driven by reduced ground contact time

(−2%) and increased hop height (+2%). These initial findings support the feasibility of operant conditioning the SSR during a dynamic SSC behavior. We plan to extend this approach to more people, include control groups, examine inter-individual variability, and determine whether SSR up-conditioning during hopping can enhance performance of other high-velocity SSC tasks, such as drop jumps.

Disclosures: J. Howaldt: None. **J.A. Brangaccio:** None. **L. Ruggiero:** None. **A.K. Chetouani:** None. **J. Hill:** None. **J.S. Carp:** None. **T.M. Vaughan:** None. **J.R. Wolpaw:** None. **M. Gruber:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.19/GG8

Topic: F.06. Posture and Gait

Title: Perturbation-Enhanced Task-Specific Training Improves Sensorimotor Adaptation, Reactive Postural Control, and Executive Function in Older Adults

Authors: *S. GUL[1], R. FATIMA[2];
[1]Dept. of Rehabil. Sci., Shifa Tameer-e-Millat Univ., Islamabad, Pakistan; [2]Dept. of Rehabil. Sci., Shifa Tameer-e-Millat Univ., ISLAMABAD, Pakistan

Abstract: Reactive postural control and fall susceptibility are related to age-related decline in sensorimotor integration and executive function. Exposure to unanticipated balance disturbances on repeated trials could facilitate adaptive motor responses and improve neural mechanisms for recovering from balance disturbances. This randomized controlled trial investigated the effects of task-specific training (TST) and yoga-based training, with and without perturbation, on reactive postural control, lower-limb strength, and executive function in older adults. Community-dwelling adults aged ≥60 years (n=204; mean age = 70.3 ± .5 years; 103 females, 101 males) with Mini-Mental State Examination scores >25 and Fall Risk Assessment Tool scores <15 were randomly assigned to TST, yoga-based training, TST with perturbation (TSTWP), or yoga with perturbation (YPWP). The participants took part in 40-minute sessions three times weekly for 12 weeks under supervision. The Mini-Balance Evaluation Systems Test (Mini-BESTest), Manual Release from Lean Test (MRLT), 30-second Sit-to-Stand Test, Manual Muscle Testing and Stroop Test were used to assess outcomes at baseline, post intervention and 1-month follow-up. Two-way repeated-measures ANOVA revealed significant time × group interactions for Mini-BESTest performance ($F(6,366)=33.838$, $p<0.001$, $\eta^2=.357$), reactive balance responses measured by MRLT ($F=20.068$, $p<0.001$, $\eta^2=.248$), and lower-limb strength ($F=40.650$, $p<0.001$, $\eta^2=.400$). There was a large improvement in reactive postural control with TSTWP scores rising from 18.61±1.90 to 22.72±1.89 at the follow-up, which was consistent, and there was a large improvement in Sit-to-Stand, which went from 9.22±2.13 to 13.08±2.19 repetitions. In contrast,

YPWP demonstrated the largest gains in executive function, showing the fastest Stroop response times (0.3376±0.0441 s post-intervention) and the fewest response errors (1.24±0.43). Improvements were retained at one-month follow-up. These results suggest that perturbations can be used to enhance adaptive sensorimotor control and cognitive-motor performance in the older population. Task-specific perturbation training specifically leads to an increase in lower limb strength and reactive postural control, whereas perturbation-enhanced yoga seems to produce a more significant effect on executive function, suggesting different mechanisms of motor and cognitive adaptation during aging.

Disclosures: S. Gul: None. **R. Fatima:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.20/GG9

Topic: F.06. Posture and Gait

Title: Influence of arm position on lower limb coordination during drop landings

Authors: *S. A. MANNELLO, H. E. MUSIC;
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Abstract: Drop landings have been used to examine sport-like landing movements often associated with anterior cruciate ligament (ACL) injuries. Utilization of sport specific arm positions has shown differences in lower extremity kinematics, specifically the extent of joint rotation at the hip and knee. However, it is unknown how different arm positions influence joint coordination patterns typically used to evaluate injury risk. While these movements are often evaluated with double-leg landings, non-contact sport injuries to the ACL often occur during tasks requiring higher loading in one limb. Therefore, the purpose of this study was to examine how changing arm position influences coordination patterns in the lower extremity for both single and double leg landings tasks. Methods: Ten healthy adults (5 Male, 32±9 yrs., 178±9 cm, 77±12 kg) performed three double and single leg drop landings from 30 cm in each of four arm conditions: free arm (FA), hands on hips (HH), arms across chest (AC), and arms overhead (AO). Kinematic and kinetic data were recorded and analyzed. For each drop landing, initial contact was defined as vertical ground reaction force >20N. Intersegmental coordination strategies were defined by calculating coupling angle patterns across the hip, knee, and ankle joints in the frontal and sagittal planes. Strategies were defined using circular statistics as in-phase and antiphase when joints rotate with similar amplitudes in the same direction or different directions, respectively, or proximal or distal dominant when amplitudes differ. Mean coupling angles were computed for each of the following joint pairs: hip frontal-knee frontal (HfKf), hip sagittal-knee frontal, hip sagittal-knee sagittal, knee frontal-ankle frontal, knee sagittal-ankle frontal (KsAf), knee sagittal-ankle sagittal. Results: Repeated measures ANOVA revealed a

significant effect of arm condition for single-leg landing KsAf ($F = 4.32$, $p < .05$). There were no other effects of arm condition. For the double-leg condition, there was a significant difference between limb patterns for HfKf ($p < .05$). Discussion: The effect of restricting arm motion (AC and HH) increased antiphase and distal (ankle) dominant coupling patterns across the knee and ankle. When arms moved freely or overhead increased in-phase and proximal (knee) dominant coordination patterns occurred. For double-leg landings, frontal plane hip-knee coordination was characterized by more in-phase coupling in the non-dominant limb. Arm condition did not broadly alter lower-limb coordination but specifically influenced multi-planar coupling between knee and ankle segments during task requiring elevated stability.

Disclosures: S.A. Mannello: None. **H.E. Music:** None.

Poster

PSTR236: Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR236.21/GG10

Topic: F.06. Posture and Gait

Title: Whole Body Angular Momentum is Modulated by Arm Position during Drop Landing

Authors: *H. E. MUSIC[1], S. A. MANNELLO[2];
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Abstract: Whole-body angular momentum (WBAM) has been used as a measure of dynamic stability as it accounts for intersegmental movements about the center of mass (COM). Modulation of WBAM increases maneuverability and balance, but the contribution of the arms to the modulation of WBAM during drop landings is unclear. Historically the arms have been ignored, strictly constrained during testing or not reported. Some sport movements inherently constrain arm movement based on the goal and involvement of objects. Since drop landings are used to simulate these sport movements, the effect of the arms is particularly relevant. Therefore, the purpose of this study was to examine the effect of arm position on WBAM during drop landings. Our hypothesis was that the arms modulate WBAM during drop landings. We expected greater WBAM changes during the free arm condition than the other conditions due to the ability to use the arms to control the COM. Methods: Eleven adults (5 Male, 31±9 yrs., 177±9 cm, 77±11 kg) completed double leg (DL) and single leg (SL) drop landing tasks from 30cm. Kinematic (VICON, Denver, CO) and kinetic (AMTI, Watertown, MA) data were measured during four arm conditions: free arm (FA), hands on hips (HH), arms across chest (AC), and arms overhead (AO). For each drop landing, initial contact (IC) was defined as vertical ground reaction force (GRFv) > 20N. WBAM was calculated for each drop landing for the entire trial and over each landing phase: loading phase, from initial contact to peak GRFv, attenuation phase, from peak GRFv to local min GRFv, control phase, from local min GRFv to steady state GRFv, and stability phase, from steady state GRFv to the end of the trial. WBAM excursion

(ΔWBAM) was calculated as the difference between maximum peak WBAM and WBAM at IC. Repeated measures ANOVA were performed to determine if average WBAM and ΔWBAM differed between the landing conditions over the entire landing phase in each plane and during each landing phase in each plane. Results: There was a significant effect of arm condition on WBAM over the entire landing phase in the frontal-plane($F(7,70) = 5.04$, $p = 0.007$). However, frontal-plane ΔWBAM did not differ among arm conditions($F(7,70)=0.82$, $p=0.572$). The transverse-plane showed a trend towards significance($F(7,70)=2.465$, $p=0.080$), with a similar non-significant effect for ΔWBAM($F(7,70)=1.98$, $p=0.184$). This indicates upper-extremity positioning alters WBAM regulation during drop landings, but not the magnitude of WBAM. Discussion: Arm position had limited effects on average WBAM. DL conditions produced greater WBAM magnitude than SL conditions. Landing type and landing phase may have a greater impact on WBAM than arm position.

Disclosures: H.E. Music: None. **S.A. Mannello:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.01/GG11

Topic: G.01. Neuroethology

Support: NIH R01NS133654-01
NSF IOS 2227963

Title: Volume EM reconstructions reveal diverse cell types, structural plasticity, and three distinct neural circuit motifs in the rhinophore ganglion of a gastropod mollusc

Authors: A. M. COOK[1], H. H. SANT[3], S. J. CASTONGUAY[1], I. K. GOETZ[1], L. CARAMELLO[1], S. BUDAKOTI[1], Y. WU[4], R. SCHALEK[4], J. W. LICHTMAN[4], *P. S. KATZ[2]; [1]Biol., [2]Univ. of Massachusetts, Amherst, Amherst, MA; [3]Biol., Col. of the Holy Cross, Worcester, MA; [4]Mol. and Cell Biol., Harvard Univ., Cambridge, MA

Abstract: Gastropod molluscs, such as *Aplysia*, *Tritonia*, and *Lymnaea*, have been important for neural circuit studies due to their large, identifiable neurons that are amenable to electrophysiological recording. Though considerable effort has gone toward mapping circuits composed of large neurons, the vast majority of small neurons have not been included. Here we used a volume electron microscopy (vEM) dataset to determine the features of neural circuits in the rhinophore ganglion (*rhg*) of the gastropod, *Berghia stephanieae*. The *rhg* sits at the base of the rhinophore, the main olfactory tentacle, presumably playing a role in olfactory processing. The neurons and circuitry of the *rhg* have been enigmatic because the neurons are smaller (<10 μm diameter) than in other ganglia. Neurons and glia were reconstructed in Neuroglancer and VAST from segmentations of the 4700 sections (33nm thick) scanned with 4x4nm resolution. In addition to thousands of afferent axons arising from the rhinophore and efferent axons arising

from the connective to the cerebral ganglion, we determined that the *rhg* contained about 9000 cells of which 90% were neurons. We fully reconstructed over 600 neurons including 192 projection neurons with an axon that traveled into the connective and 332 local interneurons whose branches were confined to the *rhg*. Three distinct neural circuit motifs were uncovered. Two motifs were variations of an olfactory glomerulus with afferent axons synapsing on projection neurons. However, the two glomeruli were distinct from each other; one had no interneurons and the afferents projected further into the brain, whereas the other contained interneurons and the afferents terminated on the projection neuron dendrites. The third motif was more complex; it contained two domains, one that was dominated by efferent peptidergic axon terminals and the other that had synapses between projection neurons and interneurons. The interneurons received afferent input. In addition to these circuits, there was evidence for immature neurons with growth cones and pruning of axons, consistent with a dynamically growing ganglion. Together, these findings reveal complex organizational features suggestive of higher order sensory processing in an understudied molluscan ganglion.

Disclosures: A.M. Cook: None. **H.H. Sant:** None. **S.J. Castonguay:** None. **I.K. Goetz:** None. **L. Caramello:** None. **S. Budakoti:** None. **Y. Wu:** None. **R. Schalek:** None. **J.W. Lichtman:** None. **P.S. Katz:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.02/GG12

Topic: G.01. Neuroethology

Support: NIH Grant 5F32AG081056-03

Title: Tardigrades use Neuroligin-4 to fortify their nervous system, rendering them resilient to large-scale anisotropic volumetric changes during anoxic and hyperosmotic stress responses

Authors: *M. J. KIRK;
Univ. of California, Santa Barbara, Goleta, CA

Abstract: Extremotolerance, the ability to survive environmental extremes, is a rare convergently evolved adaptation found across all kingdoms of life. A premier example is found in tardigrades, which are renowned for their broad extremotolerant repertoire, including resistance to ~1,000 times the human lethal dose of ionizing radiation, hyperosmotic stress, near-complete desiccation, and near-complete anoxia. The diminutive tardigrade nervous system consists of an estimated few hundred neurons, yet supports a diverse behavioral repertoire, including sensory-motor navigational strategies akin to those of Drosophila melanogaster larvae, valence-derived associative learning, and complex gaits coordinated across eight legs. We assessed the anatomical, behavioral, and molecular changes that the tardigrade nervous system undergoes during transitions into and recovery from extreme osmotic (500 mOsm, 2 hours),

anoxic (0.05 ppm, 16 hours), and freezing (−20°C, 1 hour) stressors. Via immunohistochemical analysis of synapsin-stained animals, we observed a nearly two-fold expansion in the anisotropic volume of the central brain and ventral nerve ganglia under anoxic conditions. A similar magnitude of volumetric expansion was also observed during recovery from osmotic stress. Beta-tubulin staining revealed contraction, folding, and coiling of interganglion connectives in the osmotic stress state, and their robust extension under anoxic stress. Despite these large-scale neuroanatomical changes, animals recovered to baseline velocity and locomotion within minutes, as monitored by our new behavioral tracking module, Tardigrade Tracker. Furthermore, complex motor tasks such as self-righting were unaffected in both rate and motor program, as compared to pre-stress and unstressed controls. These observations suggest that these anatomical alterations and the subsequent tensile and shear forces arising during stress exposure have minimal impact on tardigrade nervous system function. To assess the molecular mechanism of this resilience, we identified synaptic and synaptogenic proteins that are highly upregulated (10- to 400-fold) in response to stress, and found that RNAi knockdown of Neuroligin-4 significantly increased death rates and resulted in severe, prolonged motor dysfunction in animals that did survive. Together, our data provide the first evidence that the tardigrade nervous system is dramatically remodeled during transitions into cryptobiotic states, in part by using Neuroligin-4-dependent fortification to prevent significant loss of neural circuit function and ultimately enabling rapid recovery from extreme stressors.

Disclosures: M.J. Kirk: None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.03/GG13

Topic: G.01. Neuroethology

Support: NSF Cooperative Agreement OIA-2242771

Title: Regeneration of central ring ganglia in the nudibranch Berghia stephanieae

Authors: *S. GERGES, C. TAIT;
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Abstract: Gastropods are useful models for testing the limits of motor nervous system recovery because they have a centralized brain that may regenerate, and an extensive peripheral nervous system that may engage in compensatory mechanisms for regain of function. The gastropod nudibranch *Berghia stephanieae* exhibits regenerative abilities in many parts of its body, including sensory appendages. Other gastropod species have even shown limited central nervous system regeneration. Therefore, following lesioning of the pedal ganglion, the brain region most responsible for locomotion in *B. stephanieae*, we predict that we will see behavioral recovery over time via one of two mechanisms: either 1) the remaining parts of their central brain or

peripheral nervous system compensate for the functions of the missing ganglion or 2) complete regain of locomotory function will occur only when the pedal ganglion regenerates. When we lesioned the right pedal ganglion, we quantified locomotory behavior in response to a food stimulus of lesioned *Berghia* using an open arena test and automated tracking. Two days after lesion, they showed minimal movement. When they were exposed to food one week later, they exhibited high-speed circling behavior in only one direction but were unable to navigate to the food successfully. After 4 weeks, significant recovery was observed. This was indicated by several characteristics of their trajectories, such as their speed and straightness index. By the end of the 4 weeks, those measurements were close to unlesioned control *Berghia*, suggesting that they can recover behaviorally from CNS lesioning. To understand the neural changes giving rise to behavioral recovery, cryosections of whole lesioned *Berghia* including their brain and their body, to capture innervation of their foot, underwent fluorescent immunohistochemistry. Our immunohistochemistry protocol included antibodies for the neurotransmitters serotonin and small cardioactive peptide, to visualize the neural connections between the pedal ganglion and the foot. Our future directions include implementing different antibody markers for newly synthesized and proliferating neural cells.

Disclosures: S. Gerges: None. **C. Tait:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.04/GG14

Topic: G.01. Neuroethology

Support: NSF Cooperative Agreement OIA-2242771

Title: Patterns of neural activation in the nudibranch brain after chemosensory stimulation

Authors: *A. GANGULY, C. TAIT;
Biol. Sci., Marshall Univ., Huntington, WV

Abstract: The transformation of sensory input into motor output during complex adaptive behaviors has been a black box, with mechanistic studies limited to a few model systems. With the explosion of genomic and transcriptomic datasets, and the rise in techniques that can be applied to understudied taxa, like in-situ hybridization chain reaction (HCR), studying other organisms engaged in naturalistic behaviors is increasingly feasible. The nudibranch *Berghia stephanieae* is a useful model to study sensory-motor transformation in the brain, because its compact central nervous system contains fewer than 20,000 neurons and its small size supports whole mount molecular imaging. Here, we have developed an immediate early gene (IEG) based neural activity mapping protocol using fluorescent HCR to label *Egr1* expression in whole mount brains. We used homogenized *Aiptasia* sea anemones, the sole prey of *B. stephanieae*, as the chemosensory stimulus. Protocol optimization included adding overnight acclimatization of

the nudibranchs in the same set-up where stimulation would occur, shortening the anesthesia time to enable fixation of whole heads immediately after stimulation, and dissecting brains only after fixation. With this refined protocol, HCR showed consistent food cue specific increases in the number of neurons expressing *Egr1* at 30 and 45 minutes post-stimulus, with strongest labeling in the rhinophore ganglia and top edge of the cerebropleural ganglia. Rhinophore ganglion neurons were not seen to be activated at all in control individuals and if fixation occurred after only 15 minutes of food cue exposure. A large, consistently *Egr1*-positive cerebropleural neuron has been confirmed through HCR co-labeling for tryptophan hydroxylase as the giant metacerebral cell of gastropods. Ongoing experiments extend this time course to 60 and 90 minutes to test whether the upregulation propagates from the sensory rhinophore ganglia to other CNS regions, including the pedal ganglia, which contains motor neurons controlling locomotory behavior. Further experiments will compare *Egr1* expression patterns during active feeding on anemones with our chemosensory results. This work establishes *Egr1* HCR as a molecular framework for connecting sensory stimuli to neural activation patterns in *Berghia*, with the potential to explore activation of motor behaviors as well, breaking open the black box of sensory-motor transformation in this small, accessible gastropod nervous system.

Disclosures: A. Ganguly: None. **C. Tait:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.05/GG15

Topic: G.01. Neuroethology

Support: NSF grant # 2212591
NIGMS # 2P20GM103432
Wyoming Research Scholars Program

Title: Individual Xenopus tadpoles display distinct and enduring visual preferences

Authors: *C. J. BARRUS[1], K. ZHENG[2], B. BENDER[1], K. G. PRATT[3];
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Abstract: How neurons self-assemble into circuits that give rise to behaviors is a fundamental question in neuroscience. We address this question in the visual system of the *Xenopus laevis* tadpole. Xenopus tadpoles begin displaying several innate visually guided behaviors by developmental stage 48 - just 10 days postfertilization. These behaviors include a preference for green over light, and light over dark. Until now, these preferences have been studied by measuring the behavior of groups of tadpoles. The overall behavior of the group, however, does not reflect the behavior of individuals. Therefore, here we studied visual preferences displayed by individual tadpoles. Our data show that individual tadpoles, even of the same clutch,

displayed varied behavior relative to one another: some tadpoles displayed a strong preference for light over dark while others preferred dark over light; some displayed a strong preference for green over light while others preferred light over green. While preferences varied across tadpoles, preferences displayed by a given individual were stable over time (i.e. enduring). Also, previous work on groups of tadpoles shows that visual preferences are shaped by the neuromodulator serotonin (5HT). At the single tadpole level, we found that inhibiting 5HT by exposing tadpoles to a tryptophan hydroxylase inhibitor weakened the preference for light displayed by the majority of individuals (similar to the group behavior), and that enhancing endogenous serotonin transmission by exposing tadpoles to a selective serotonin reuptake inhibitor strengthened the preference for light displayed by the majority of individuals (also similar to the group behavior). However, by studying individuals, we also identified a small subset of tadpoles that displayed an exceptionally strong, 5HT-independent preference for light.

Disclosures: C.J. Barrus: None. **K. Zheng:** None. **B. Bender:** None. **K.G. Pratt:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.06/GG16

Topic: G.01. Neuroethology

Support: NSF-IOS #2016188

Title: Altered internal and external states differentially modulate in-flight visuomotor behavior across Drosophila species

Authors: *T. YE[1], R. EGAL[1], S. BUTTORFF[1], M. KELES[2], S. M. WASSERMAN[1];
[1]Neurosci., Wellesley Col., Wellesley, MA; [2]Johns Hopkins Univ., Baltimore, MD

Abstract: To make a decision that supports survival, organisms must be flexible, assigning value to salient sensory stimuli that aligns with varied internal and external states. To study this flexibility, we utilize a comparative approach examining flight behavior across Drosophila species native to different ecological habitats. We investigate vision-based perception through characterization of body saccades in response to internal and external cues using the magnetic tether flight arena. When presented with an oscillating bar against a textured background, cosmopolitan D. melanogaster adopt a hybrid fixate-or-saccade strategy, fixating on the background in-between wide bar-tracking saccades. Desert-native D. mojavensis, however, utilize a fused strategy, integrating saccade and stabilization pathways for fluid visual tracking (Rimniceanu, et al., 2024). While cosmopolitan flies have flexible visuomotor responses, switching between smooth and saccadic tracking based on environmental cues, desert flies demonstrate less flexibility. These differences may reflect the stress-resilient neural architecture of desert species designed to promote survival in a harsh environment. To elucidate how desert species integrate internal and external cues, we investigated whether desert flies are able to

generate flexible visuomotor behavior under an altered internal state via sleep deprivation. Baseline sleep characterization revealed that desert flies had increased total sleep and faster homeostatic rebound compared to cosmopolitan flies. Baseline (uninterrupted sleep) and sleep-deprived flies were presented with a featureless (uniform) and high-contrast visual background. Baseline cosmopolitan flies exhibited a significant increase in saccade frequency against a uniform background compared to a high-contrast background. By contrast, baseline desert flies had infrequent saccadic response and robust stabilization across both conditions. Neither group altered saccadic behavior in response to reduced background intensity indicating that both may further employ a contrast-gain approach to assist in perception under low-light conditions. In a uniform background, sleep-deprived cosmopolitan flies demonstrated decreased saccadic frequency while sleep-deprived desert flies had a slight increase in saccadic frequency compared to baseline controls. By assessing the effects of sleep deprivation, we hope to understand how internal cues may induce flexible visuomotor behavior in desert flies. This work will shed light on the adaptive nature of visual circuits to deepen our understanding of state-dependent decision-making.

Disclosures: T. Ye: None. **R. Egal:** None. **S. Buttorff:** None. **M. Keles:** None. **S.M. Wasserman:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.07/GG17

Topic: G.01. Neuroethology

Support: NSF Cooperative Agreement OIA-2242771

Title: In-situ hybridization chain reaction to investigate olfactory activation in Rhagoletis pomonella fruit flies

Authors: *K. GARCIA, H. BUNDY, C. TAIT;
Biol. Sci., Marshall Univ., Huntington, WV

Abstract: Fruit flies use specific olfactory circuits traveling from their antennae to their brain to find appropriate fruits to lay eggs within. For this study, it was our goal to validate fluorescent in-situ hybridization chain reaction (HCR) to mark neuron types and neural activation via gene expression in the brain of *Rhagoletis pomonella*, the apple maggot fly. This tephritid fly has long been studied in evolutionary biology and is an important agricultural pest that uses olfaction to find host fruit, but has yet to be examined at the level of single neurons using molecular techniques. To explore the use of HCR for immediate early gene (IEG) expression as a proxy for visualizing neural activity, we first exposed *R. pomonella* to 10 minutes of volatiles found within natural host fruits of the species. Both male and female *R. pomonella* were used, as well as different host-fruit associated populations targeting apple, hawthorn, and dogwood fruit. Flies

were immediately euthanized and fixed after stimulation. After fixation, brains were dissected. Using HCR, we targeted the IEG *stripe (EGR-1)*, used previously in *D. melanogaster* and in honeybees, to mark neural activity. Labeling for expression of this gene shows the pattern of activation across the brain in response to the specific odor tested. Simultaneously, we visualized *tryptophan hydroxylase (TrHy)* positive neurons to show proof of concept for identifying specific populations of neurons in the *Rhagoletis* brain. *TrHy* is the rate-determining enzyme that produces serotonin in insects, thus in these same odor-stimulated flies, we could identify all serotonergic neurons. We also used FIJI software to count *TrHy* positive neurons in the brain. Our results show extensive activation via *stripe* expression in response to all odors tested, in both sexes of flies, and across populations. Further refinement of our technique is required, namely co-labeling with specific gene markers, to focus our analysis on neurons in olfactory pathways and allow for comparisons across sexes and species. After labelling for *TrHy* expression, we saw several neurons that were co-labeled for *stripe* and *TrHy*, mostly in the subesophageal ganglion, indicating these neurons were active during odor stimulation. We then produced a map of the serotonergic neural clusters from our cell counts and compared it to previously published maps for *D. melanogaster*. Differences in number and location of clusters were seen between *Rhagoletis* and *Drosophila*, and future analysis will explore potential differences between the *Rhagoletis* sexes and populations.

Disclosures: K. Garcia: None. **H. Bundy:** None. **C. Tait:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.08/GG18

Topic: G.01. Neuroethology

Support: NEI Grant K99EY036889
NEI Grant K99EY036123
NEI Grant R01EY026031

Title: Interplay between chemical and electrical synapses for visual orientation

Authors: *G. FRIGHETTO[1], M. DOMBROVSKI[2], L. PALACIOS CASTILLO[1], P. SANFILIPPO[2], S. L. ZIPURSKY[2], M. A. FRYE[1];
[1]Integrative Biol. and Physiol., [2]Biol. Chem., UCLA, Los Angeles, CA

Abstract: The detection of salient visual objects and the selection of appropriate behaviors are fundamental to survival in many animals. The fruit fly has proven to be a productive model organism for understanding how a compact visual circuit detects a looming threat and commands an escape response. Conversely, how flies perceive and orient toward an attractive visual feature is poorly understood. We previously showed that a type of columnar visual feature detecting neurons, T3, is required for saccadic orientation toward landscape features during flight. Here,

we examined the downstream partners of T3 in a neuropil called lobula. By exploring fly optic lobe chemical synaptic connectomes, we identified a specific type of visual projection neurons, LC17, that receives excitatory T3 inputs and sends outputs to the central brain. We then investigated their physiological properties, tested their functional connectivity with T3, and their behavioral role in controlling visual orientation behavior. Our results show that these visual projection neurons are functionally connected to T3, well-suited for processing visual objects that elicit attraction, and part of a visual pathway for saccadic orientation behavior during flight. Unexpectedly, we discovered that this circuit heavily relies on both chemical and electrical synapses. Behavioral, molecular, and physiological analyses confirm that gap junctions are highly expressed in LC17 neurons and required for saccadic object orientation. These results cast light on the enigmatic neural circuits underlying innate visual orientation behavior, and the complex interplay between chemical and electrical transmission modes that support rapid visual object detection and gaze orientation.

Disclosures: G. Frighetto: None. **M. Dombrovski:** None. **L. Palacios Castillo:** None. **P. Sanfilippo:** None. **S.L. Zipursky:** None. **M.A. Frye:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.09/GG19

Topic: G.01. Neuroethology

Support: NIH Grant 5K99EY035504
NIH Grant 4R00EY035504

Title: Impact of social isolation on the neural responses of a wasp with identity recognition

Authors: *C. JERNIGAN[1], W. FREIWALD[2], M. SHEEHAN[3];
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Abstract: *Polistes fuscatus* wasps possess individually distinctive color patterns on their face, which they can use to visually recognize and discriminate each other. The development of this ability is dependent upon social experience. Previously, we found a localized physiological population of neurons, we refer to as *wasp cells*, in *Polistes fuscatus* that are selective to forward-facing wasp images in the lateral protocerebrum. Additionally, the synaptic volumes of high-order visual centers in these same brain areas are differentially impacted by social experience. We now perform multichannel extracellular electrophysiology recordings in the brains of *P. fuscatus* wasps that have been isolated for their entire adult lives and have never seen another adult wasp. We find a striking difference in the relationship between the selectivity for forward-facing wasp images with and without color across the brains of these animals. In normally reared animals there is a very tight relationship between a unit's selectivity for wasp

shape with and without wasp internal features present. Here in isolated animals this relationship is almost entirely gone. However, we do still find units that are selective for forward facing wasp images with and without internal wasp features. This suggests that there is a developmental program in *Polistes fuscatus* that produces *wasp cells* in appropriate regions of the brain and experience is not necessary for social image selectivity to develop in these circuits. However, the proportion of selective units and their degree of selectivity to different wasp features is impacted by social experience. This finding suggests that connectivity between circuits responding to wasp shape and wasp color features may be what is altered by social experience, and ultimately gives rise to the different social discrimination abilities between socially reared and socially isolated animals.

Disclosures: C. Jernigan: None. **W. Freiwald:** None. **M. Sheehan:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.10/GG20

Topic: G.01. Neuroethology

Support: TUBITAK Grant 123E155

Title: Closed-Loop State Estimation Using Heterogeneous Leaky Integrate-and-Fire Neuron Populations

Authors: *E. GÖRAL[1], I. UYANIK[2];
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Abstract: Biological nervous systems achieve robust state estimation and feedback control within uncertain environments by encoding sensory data into sparse, asynchronous spike trains distributed across neural populations. Unlike conventional robotic systems that rely on time-sampled digital feedback, biological organisms mediate sensing and action through coordinated population spiking. This motivates computational frameworks that operate directly on neural representations. We propose an online, closed-loop state estimation architecture inspired by neurophysiological recordings from *Apteronotus leptorhynchus* during refuge-tracking tasks. In the neural recordings, distinct neuronal subpopulations exhibit activity that correlates directly with kinematic signals such as relative position and velocity. To mimic this mechanism, our framework encodes relative tracking signals into complementary subpopulations of Leaky Integrate-and-Fire (LIF) neurons. The resulting spike timings are converted into causal firing-rate estimates, decoded via a maximum-likelihood population estimator, and integrated through a Kalman filter to generate smooth error estimates suitable for real-time feedback control. We validate this online architecture using a simulation of a reference-tracking task of the weakly electric fish. Our simulation results demonstrate that even under noisy conditions, spiking-neuron populations preserve sufficient information to extract position and velocity signals,

enabling stable closed-loop control when paired with a classic proportional-derivative controller. Future work will focus on integrating empirical neural recordings from *A. leptorhynchus* directly into this framework, incorporating heterogeneous sensory encoding neurons to better characterize the underlying mechanisms of biological state estimation. Ultimately, this work offers a control-theoretic perspective on the transformation of spike-based sensory representations into actionable internal states, with broader implications for understanding neural computation and advancing neuromorphic sensing, active perception, and brain-machine interfaces.

Disclosures: E. Göral: None. **I. Uyanik:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.11/GG21

Topic: G.01. Neuroethology

Support: NSF Cooperative Agreement OIA-2242771

Title: Investigating olfaction in Rhagoletis pomonella using receptor modeling, in-situ hybridization, and electrophysiology

Authors: *J. LIN, C. TAIT;
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Abstract: *Rhagoletis pomonella* is a specialist tephritid fly, with individual host-associated populations infesting different fruits including apples, hawthorns, and dogwoods. Much is known about the evolutionary relationships of these populations, as well as their host fruit discrimination behavior facilitated by their olfactory system. Specific single volatiles that are behaviorally relevant to these specialists have been characterized in flight tunnel assays. However, the specific mechanisms and circuits involved, and how they differ between flies that prefer different fruits, are not well known. In insects, the antenna and maxillary palps both serve as olfactory appendages. The antenna detects a wider range of fruit odors, while the palps detect a greater range of food odors. Our study examined the role of the palps in host fruit discrimination behavior in specialist *R. pomonella* through odorant receptor (OR) modeling, in-situ hybridization chain reaction (HCR) to label ORs, and electrophysiology. *R. pomonella* and *Rhagoletis zephria* ORs were modeled in AlphaFold v3 and docked in Autodock Vina. We targeted the volatile odorant 1-octen-3-ol, as this is present in hawthorn and dogwood fruit, but absent in apples and found to be aversive to apple-infesting flies in our docking studies. We chose *Rhagoletis* OR sequences to model based on expected homology to *Drosophila melanogaster* ORs. We found that OR13a requires the lowest binding energy to 1-octen-3-ol in both *Rhagoletis* species due to similar intermolecular forces despite binding pocket residues changes. Both OR85b and OR85d lacked similarities in their binding pocket residues between

the species, and in comparison to *D. melanogaster*, potentially due to being located on different appendages. We explored localization of these ORs using fluorescent HCR on both olfactory appendages. Furthermore, electroantennography (EAG) and electropalpography (EPG) were performed to record the response of *R. pomonella* olfactory appendages when exposed to fruit odors, including 1-octen-3-ol, in serial dilutions. The antenna was expected to strongly respond to butyl hexanoate, a valence-determining odor of *R. pomonella* released from apples, while the palps was expected to have a weaker response due to differences in function between appendages. We also expected responses to 1-octen-3-ol from both appendages, due to our docking and HCR results. Ultimately, our approach using multiple different techniques allows us to uncover the mechanisms underlying olfactory preference. Olfactory preference has guided evolution of these flies in the past and continues to determine their egg-laying behavior in specific fruits.

Disclosures: J. Lin: None. **C. Tait:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.12/GG22

Topic: G.01. Neuroethology

Support: TÜBİTAK 5240046

Title: A Radial Flow Arena for Dissecting Visual and Mechanosensory Contributions to Rheotaxis in Freely Swimming Adult Zebrafish

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Abstract: Multisensory integration allows animals to form coherent percepts by combining signals from multiple sensory channels. Rheotaxis—the tendency to orient against water flow—is an ethologically grounded behavior in zebrafish that relies on both lateral-line mechanosensation and vision, making it an ideal model for studying sensory reweighting under naturalistic conditions. However, most existing paradigms physically restrain animals or impose directional biases that confound behavioral interpretation. We developed a 360° radial rheotaxis arena in which adult zebrafish swim freely while a sinusoidally modulated flow field rotates around them at controlled frequencies (0.10-0.95 Hz). Radial flow geometry eliminates directional bias, ensuring continuous and uniform mechanosensory stimulation throughout the arena. A display mounted above the arena projects visual stimuli onto the swimming surface, allowing visual input to be manipulated independently of flow. High-speed videography and DeepLabCut-based pose estimation provide continuous readout of heading angle and tail kinematics. To isolate visual versus mechanosensory contributions, we compare two conditions:

a flow-with-visual condition in which drifting stripe patterns are synchronized with the rotating flow, and a flow-only condition in which the display provides uniform illumination without any moving pattern. By comparing fish heading to the tunnel reference signal across both conditions, we characterize how visual input shapes orientation accuracy and modulates mechanosensory-driven rheotaxis across a range of stimulus frequencies. This platform establishes a rigorous, fully unrestrained framework for characterizing multisensory reweighting in zebrafish and sets the stage for future circuit-level dissection of cue integration. This study was supported by TÜBİTAK (Project No: 5240046).

Disclosures: E. Öztürk: None. **N. düz:** None. **S. Anilmak:** None. **I. Uyanik:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.13/GG23

Topic: G.01. Neuroethology

Support: 1ZIAMH002950-10

Title: State-dependent gating of visual threat salience in area prostriata

Authors: *R. LINGG[1], C. ANCATEN[3], G. NNAMDI[2], K. YU[4], H. WANG[6], J. O'MALLEY[5], Y. LENG[7], H. A. TEJEDA[8], M. A. PENZO[5];
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Abstract: Internal hunger states dynamically modulate the behavior of foraging animals in complex environments with uncertain resource, or predator, densities. When starved, neuronal circuits indicating basic survival requirements bias attentional systems away from vigilance (i.e. active monitoring of animal's surroundings) and towards actions promoting survival through resource acquisition. Reduced vigilance when foraging leads to a greater chance that a threat is not detected, or that detection is delayed sufficiently to challenge the likelihood of survival when a predator is encountered. In ecological situations, threatening stimuli often arise from the visual periphery unexpectedly. Here, we characterize a limbic-cortical visual processing region known as area prostriata (APr) involved in the detection of a rapidly advancing threat from the far periphery that is uniquely sensitive to metabolic state. Using the looming visual threat task in combination with single-cell calcium imaging we show APr neurons encode the detection of visual threat, initiation of escape from overhead looming threat, and are biased toward rapid (300 °/s) stimuli occurring in the far periphery. An acute metabolic challenge of 24hr food deprivation abolished visual sensitivity in the far periphery among APr neurons, and reduced escape

probability. Follow-up experiments determined APr neurons that express pituitary adenylate cyclase-activating polypeptide (*adcyap1*: PACAP) were uniquely sensitive to the effects of food deprivation. *Ex vivo* recording of APr^{adcyap1} indicated 24hr food deprivation reduced intrinsic excitability of these neurons; an effect not observed in neighboring primary visual cortex. Chemogenetic inhibition of APr^{adcyap1} was sufficient to prevent looming-evoked escape behavior, whereas excitation could recover escape behavior among food deprived animals. Further, knock-down of serotonin synthesis in a population of median raphe (MnR) neurons that project to APr was sufficient to recapitulate the suppression of escape observed following food deprivation. *In situ* hybridization experiments revealed APr^{adcyap1} neurons in layer II/III express the serotonin receptor, *htr1a*. Further, *ex vivo* application of the selective *htr1a* antagonist, WAY100635, produced a robust suppression of excitability in APr^{adcyap1} neurons in tissue obtained from sated animals, selectively. Together, our results demonstrate APr integrates internal physiological signals with visual input to guide adaptive defensive behavior and identify a novel state-sensitive visual-limbic circuit where interoceptive dysfunction may contribute to abnormal threat processing.

Disclosures: R. Lingg: None. **C. Ancaten:** None. **G. Nnamdi:** None. **K. Yu:** None. **H. Wang:** None. **J. O'Malley:** None. **Y. Leng:** None. **H.A. Tejeda:** None. **M.A. Penzo:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.14/GG24

Topic: G.01. Neuroethology

Title: Mice use auditory information to hunt crickets

Authors: *S. MOSELEY, L. SCHUSTER, N. SHETTIGAR, J. TERAN, E. J. DENNIS; Janelia Res. Campus, Ashburn, VA

Abstract: Mice (Mus musculus) are omnivores that will readily engage in hunting behaviors when crickets are present. We developed a foraging model in which mice located hidden cricket tiles in a 2 meter wide, hexagon enclosure. The enclosure contained 157 tiles wrapped in felt where 16 of the tiles contained a hidden trap door and a speaker. Only one tile was active at a time. A cricket was hidden in the trap door and the mouse had to pause in the correct tile to gain access to the hidden compartment. To test which sensory systems the mice were using to search for crickets, we examined subject performance across multiple sensory modalities. There was a significant decrease in hunting performance when the mouse did not have access to auditory information on the cricket location. To further test how mice were using auditory information to locate cricket tiles, we manipulated sound intensity of the auditory signal and compared cricket release performance. When sound intensity was equalized, mice performance dropped indicating that some mice are using intensity of the auditory signal to locate prey. We are now investigating

how underlying neural responses from the inferior colliculus to varying acoustic parameters predict behavioral performance during this freely moving, complex behavioral task.

Disclosures: S. Moseley: None. **L. Schuster:** None. **N. Shettigar:** None. **J. Teran:** None. **E.J. Dennis:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.15/HH1

Topic: G.01. Neuroethology

Title: The effect of song familiarity on song-evoked pS6 activation of the caudolateral nidopallium (NCL) in the adult male zebra finch

Authors: *M. FERNANDEZ-VARGAS[1], C. GRUSCHOW[2], C. LIPPERT[2], A. DAO[1], Z. LEVINE[1], M. MOLINA[1], J. VALENCIA[1];
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Abstract: Conspecific song induces neural activation in nidopallial and mesopallial regions of the zebra finch brain. While the caudomedial nidopallium (NCM) and caudomedial mesopallium (CMM) have been widely studied in song acquisition and adult song perception, the role of the caudolateral nidopallium (NCL), a region thought to exert executive control and adaptive behavior, remains less understood in songbirds. This study investigated phosphorylated protein S6, a molecular marker of neuronal activation, in subregions of the NCM, NCL, and CMM as well as the HVC of adult zebra finch males following 30 m of playback of novel, familiar conspecific songs (male cage mate) or silence. It was found that, relative to silence, the NCM and NCL are reliably activated in response to novel songs. Familiar songs failed to significantly activate the NCM and NCL relative to silence, though marginal significance was found in some cases. This response is found both dorsally and ventrally across the NCM and NCL and the dorsal regions consistently showed higher activation than the ventral regions. Beyond 1.5 mm laterally from midline, novel songs activation in the NCL extends caudodorsally until 2.7 mm from the midline, but the ventral NCL stream of activation weakens from 1.7-2.7 mm. The CMM, HVC, and dorsal-rostral NCL (a subregion rostral to HVC) did not show differential activation across acoustic conditions. These results suggest a dorsal and ventral stream of conspecific song processing that extends from the NCM through the NCL medially to laterally. These findings suggest coordinated medial-to-lateral processing of conspecific song and supporting roles for the NCM and NCL in encoding song novelty, familiarity, and possible memory consolidation.

Disclosures: M. Fernandez-Vargas: None. **C. Gruschow:** None. **C. Lippert:** None. **A. Dao:** None. **Z. Levine:** None. **M. Molina:** None. **J. Valencia:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.16/HH2

Topic: G.01. Neuroethology

Support: CSIR Fellowship, Govt of India
MoE Fellowship, Govt of India
Prime Ministers Research Fellowship, Govt of India
ICMR fellowship, Govt of India
UGC Fellowship, Govt of India
DBT/Wellcome Trust India Alliance Senior Fellowship
Indian Institute of Science internal grants
Google Asia Pacific research grant
Intramural grant from Pratiksha Trusts Initiatives

Title: Natural behavior elicits reliable neural signatures in high-level sensory and motor regions of freely moving monkeys

Authors: *S. MUNDA[1], S. SIMON[1], S. SAHA[1], J. JOBY[1,2], T. CHERIAN[1], G. JACOB[1], J. DAS[1], D. BHADRA[1], S. P. ARUN[1];
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Abstract: It is widely believed that neural activity during real-world vision is either fundamentally different or more variable compared to controlled screen-based tasks. This is because each trial in a real-world task is not repeatable and could involve additional influences due to eye, head and body position variations. Alternatively, natural behaviors might elicit reliable neural signatures in high-level visual and motor regions which contain invariant representations. To address this fundamental gap in our knowledge, we developed a naturalistic environment consisting of a large arena to study real-world vision and a touchscreen workstation with gaze tracking to study screen-based vision in a more controlled setting. We performed wireless brain recordings from inferior temporal (IT) and premotor/prefrontal (PMv/PFC) cortex of two monkeys while they performed two tasks. In the naturalistic task, they moved freely through a naturalistic environment to take different food rewards offered by different experimenters across many trials. In the fixation task, monkeys viewed images of natural objects while they voluntarily rested their head on a chinrest. To investigate visual information present in each task, we trained linear decoders on the recorded neural population to infer the food & experimenter identity on each trial of the natural task. Our main findings are as follows: (1) Food was decodable only from IT during the fixation task but from IT & PMv during the natural task, presumably because different foods involved different grasps; experimenter identity could be reliably decoded from IT in both tasks; (2) Food & experimenter identity during the naturalistic task could be reliably decoded using decoders trained on the fixation task, but only at specific event times; (3) Neural responses were more variable in natural task across the IT, PMv & PFC, but food & experimenter information was equally reliable as in the fixation task upon controlling

for the response duration and numbers of trials. Taken together, our results show that neural activity during real-world vision is as reliable as in controlled settings, and is systematically related to neural activity to images on a screen. A previous version of this work was presented at Neuroscience 2025.

Disclosures: S. Munda: None. **S. Simon:** None. **S. Saha:** None. **J. Joby:** None. **T. Cherian:** None. **G. Jacob:** None. **J. Das:** None. **D. Bhadra:** None. **S.P. Arun:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.17/HH3

Topic: G.01. Neuroethology

Support: Helen Hay Whitney Foundation
Searle Scholars Award
Klingenstein-Simons Fellowship in Neuroscience
Kavli Institute for Brain and Mind
NIH R00MH112840
Packard Foundation Fellowship
Pew Biomedical Scholar Award
McKnight Scholars Award

Title: Hunger reshapes sensory feature selectivity to promote food seeking

Authors: *K. MARTIN[1], E. DEAN[2], M. LOVETT-BARRON[3];
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Abstract: To generate adaptive behavior, animals must flexibly prioritize sensory information relevant to their physiological needs (e.g. representation of food when hungry). However, how internal physiological state reshapes sensory circuits to bias ethologically-relevant behavior remains poorly understood. Here, we examine how hunger modulates visually-driven prey capture and underlying sensorimotor circuits in larval zebrafish. We asked whether hunger alters neural representation of specific ethologically-relevant prey features, including color, size, and movement kinematics, and how these changes influence food-seeking strategies.In freely moving fish, hunger broadened prey selection. Sated and hungry animals both consumed small ultraviolet-reflective microorganisms (paramecium), but only hungry fish additionally targeted larger, red/orange microorganisms that move with different motion statistics (artemia). In a head-restrained virtual prey detection assay, visual presentation of fictive prey revealed that hunger increased prey-evoked pursuit across a wide set stimulus colors, movement patterns, speeds, and size. To identify circuit-level changes underlying this behavioral expansion, we performed two-photon calcium imaging from visual areas known to be involved in prey-capture during behavior (e.g. optic tectum and pretectum/AF7). Hunger reduced both behavioral and neural selectivity,

where responses to virtual prey were not restricted the natural sensory features of common food items. Specifically, this expansion occurred at the level of individual pretectal neurons within early visual circuitry, such that neurons in hungry fish responded to a broader set of stimulus features than those in sated fish. Thus, internal state increases the range of visual features capable of driving hunting pursuit. We are currently investigating the cellular mechanisms underlying hunger-dependent modulation of visual selectivity and motor behavior.Together, these findings suggest that hunger reconfigures early sensory coding to expand the set of stimuli that engage prey-capture circuits. This state-dependent sensory reweighting may enable flexible, need-appropriate foraging strategies by lowering feature selectivity within early visual networks.

Disclosures: K. Martin: None. **E. Dean:** None. **M. Lovett-Barron:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.18/HH4

Topic: G.01. Neuroethology

Support: Wolfson College-PDN PhD Studentship
Medical Research Council
The Royal Society
Research Foundation for Opto-Science and Technology
The Ichiro Kanehara Foundation
Brain Science Foundation
PDN Small Research Grant

Title: Developing a precision task control for systems neuroscience in free-moving marmosets

Authors: *Z. PAN, J. HENLEY-WATERS, J. CHAN, K. TAMURA;
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Abstract: The common marmoset is a highly promising model for circuit physiology of visual cognition owing to its small and lissencephalic cortex compatible with high-density electrophysiology and optogenetics. While marmosets demonstrate higher task performance when allowed to behave without head fixation, effective methodologies for combining electrophysiology and optogenetics with free-moving marmosets are yet to be established. Here, we developed an integrated system that supports flexible task design, adaptive task control, and temporally precise synchronisation with external devices. To minimise the disturbance by external environments, we constructed our behavioural system within a tightly sound-insulated box with a 40 dBA attenuation. A liquid crystal screen with a 162 PPI display and 240 Hz/1 ms refresh rate, an infrared touch sensor, multiple high-speed video cameras, Python-based task control, stereo loudspeakers, and a reward pump were assembled using solid aluminium frames. Our touchscreen system presented small, fine-grained visual object stimuli with high temporal

accuracy, and detected touches by fingers and nails. 3D reconstruction of marmoset head direction with multi-angle filming allowed the estimation of marmoset's engagement during task performance. Multifunction I/O cards were connected to record all task-related electrical signals. Task events and cameras were synchronised by external timing pulses ($\sigma = 0.19$). Using this platform, we trained two marmosets in a visual object memory task and a perceptual discrimination task to dissociate memory-based and perceptual decision processes. Our task programmes allowed tailored, stepwise training processes of complex cognitive tasks with on demand and/or automatic feedback and parameter updates. Across various stages of the training, the animals stably performed several hundred trials per day without water restriction and kept consistent accuracy and reaction time, demonstrating constant progress of rule learning. We are currently combining this behavioural system with wireless electrophysiology and optogenetics to dissect causal neuronal processing for mnemonic and perceptual judgements.

Disclosures: Z. Pan: None. **J. Henley-Waters:** None. **J. Chan:** None. **K. Tamura:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.19/HH5

Topic: G.01. Neuroethology

Support: NIH T32GM133351
NIH F31NS141340
UC San Diego J. Yang Scholarship
The Taiwanese Government Scholarship to Study Abroad Award
The McKnight Pecot Fellowship
NIH R01-NS135853
Allen Discovery Center for Neurobiology in Changing Environments
Searle Scholars Award
Pew Biomedical Scholar Award
Sloan Research Fellowship
Packard Foundation Fellowship
McKnight Scholars Award
NIH DP2EY036251

Title: Hunger modulates social perception to produce adaptive group behavior

Authors: J. L. NAPOLI[1], J. YU[1], R. MUNOZ[1], C. HILTY[2], G. T. MEYERHOF[1], P. PURI[3], J. ALJADEFF[1], *M. LOVETT-BARRON[4,1];
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Abstract: Collective behaviors emerge from individuals sensing and responding to their neighbors, conferring broad advantages during predator avoidance and foraging. Within groups,

individuals are subject to changes in their internal states that can modify sensory processing and behavior, yet little is known about how state-dependent perception affects group-level behaviors. Here, we investigate how hunger influences social sensory processing and collective behavior in *Danionella cerebrum*, a micro glassfish that schools using vision and whose lifelong optical transparency enables large-scale neural imaging in behaving adults. Using multi-animal posture tracking in freely-swimming schools, we find hungry groups coordinate more strongly than sated groups, exhibiting higher heading correlation and reduced inter-individual distances across group sizes of 4-10 fish. To assess whether hunger influences individual engagement with social partners, we built a virtual reality arena to display realistic *D. cerebrum* renderings across a range of movement and appearance parameters. Hungry individuals showed markedly less selectivity than sated fish, readily engaging with virtual conspecifics moving with unnatural linear motion or reduced contrast. To investigate the neural correlates of hunger-dependent social selectivity, we used two-photon calcium imaging in adult fish viewing virtual conspecific movement. We found broader neural responses in the optic tectum and dorsal thalamus across this same stimulus range in hungry fish, while sated fish showed narrow stimulus selectivity. These results suggest hunger adaptively expands sensory tuning to socially relevant motion cues in early visual circuits. To link state-dependent interactions to group-level dynamics, we fit a stochastic model incorporating random diffusion and pairwise directional copying to measured group behavior. By examining the features of models fit to hungry or sated groups, we found that hunger enhances social interactions (i.e., rate of copying) and reduces non-social diffusion relative to sated groups. Hungry fish also explored an empty arena faster than sated fish; simulations of our model with parameters matched to each group recapitulated this difference even when controlling for swim speed, attributing the effect to inter-individual interactions. Together, these findings demonstrate that hunger reshapes sensory processing of social cues in early visual circuits to drive emergent adaptive group behavior, providing a framework for understanding how individual internal states coordinate collective action in social species.

Disclosures: J.L. Napoli: None. **J. Yu:** None. **R. Munoz:** None. **C. Hilty:** None. **G.T. Meyerhof:** None. **P. Puri:** None. **J. Aljadeff:** None. **M. Lovett-Barron:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.20/HH6

Topic: G.01. Neuroethology

Support: JSPS KAKENHI Grant JP18H05267
JSPS KAKENHI Grant JP23H05410
JSPS KAKENHI Grant JP24K09282
JSPS KAKENHI Grant JP24K23223

Title: Mating induces partner-specific memory that selectively suppresses maternal aggression in mice

Authors: *K. SAITO[1], T. ITAKURA[2,1], A. KAMBE[1], K. MURATA[1], N. KAWANO[3], T. KANEKO[4], K. TOUHARA[1];
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Abstract: In biparental mammals, females and males remain together throughout reproduction and offspring care, forming the smallest functional social unit. Because females are central to offspring care in mammals, maintaining this partnership requires females to remember and recognize their mating partners. Such partner-specific memory constitutes a fundamental form of social memory that supports family stability. This memory is expected to involve processes of formation, persistence, and recall across reproductive stages. Behavioral evidence describing these processes provides a basis for investigating the underlying neural mechanisms.
Although the laboratory mouse (*Mus musculus*) is one of the most widely used model organisms for studying social behavior and exhibits biparental care, it remains unknown whether mothers remember their mating partners. Mothers display robust aggression toward intruders, a behavior known as maternal aggression. In a biparental context, mothers would be expected to selectively tolerate their coparents. We thus hypothesized that maternal aggression would be selectively suppressed toward the mating partner. We tested this hypothesis in inbred laboratory mice.
Our results showed four main findings. First, female mice formed partner-specific memory through male-derived chemosensory cues encountered during mating. Second, this memory persisted throughout the approximately 20-day gestation period and was recalled during lactation, resulting in selective suppression of maternal aggression toward males of the partner strain. Third, mothers generated by artificial insemination lacked partner-specific memory, demonstrating that mating experience is required for its formation. Finally, the combination of male-derived chemosensory cues and genital mechanical stimulation was sufficient to induce partner-specific memory in the absence of mating.
Through a series of behavioral experiments, we revealed that mating induces partner-specific memory in female mice that remains functional during motherhood. These findings establish a framework for investigating the neural mechanisms underlying its formation, persistence, and recall.

Disclosures: K. Saito: None. **T. Itakura:** None. **A. Kambe:** None. **K. Murata:** None. **N. Kawano:** None. **T. Kaneko:** None. **K. Touhara:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.21/HH7

Topic: G.01. Neuroethology

Title: Peripheral immune signaling reshapes neural circuits underlying learned pathogen avoidance

Authors: *I. C. GRUNWALD KADOW;
Med. Faculty, Inst. of Physiol., Friedrich Wilhelms Univ. Bonn, Bonn, Germany

Abstract: Animals constantly face a fundamental dilemma: food is essential for survival, yet feeding also exposes them to potentially harmful microbes. To minimize the risk of future infection, animals rapidly adapt their feeding behavior after negative post-ingestive experiences. However, how immune detection is translated into persistent behavioral change remains poorly understood.Pathogenic food ingestion in *Drosophila melanogaster* induces a rapid transition from innate attraction towards pathogenic bacteria to learned avoidance, providing a tractable model to study how immune activation reshapes behavior. We previously identified a requirement for PGRP-LC signaling in octopaminergic neurons (OANs), antimicrobial peptides (AMPs), and mushroom body-dependent learning processes in mediating this adaptive switch[a].Our recent findings further uncover a bidirectional communication axis between the nervous system and the fat body[b], a metabolic and immune organ functionally analogous to mammalian adipose tissue and liver. Upon bacterial ingestion, immune activation in the fat body triggers an AMP-dependent response while engaging OA signaling. In turn, OAN activity induces calcium dynamics and dopamine release from adipocytes, with this systemic dopamine acting through Dop1R1 receptors in mushroom body output neurons (MBONs) to alter odor valence coding and suppress feeding on pathogen-associated food sources.Together, our findings identify a bidirectional immune-brain communication pathway in which peripheral tissues also actively reshape high-order neural circuits to drive learned adaptive behavioral change; challenging the traditional view of cognition as a purely brain-centered process. Ongoing work further investigates whether AMPs act not only as immune effectors, but also as signaling molecules capable of modulating cellular physiology and neural function through receptor-mediated calcium signaling pathways.

Disclosures: I.C. Grunwald Kadow: None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.22/HH8

Topic: E.07. Visual Sensory-Motor Processing

Support: NIE Grant R00EY032179

Title: Active sensing explains cortical variability and improves visual information

Authors: *D. P. ROWLEY[1], R. RESSMEYER[2], T. KOTHAPALLI[3], A. HUK[4], J. F. MITCHELL[5], D. A. BUTTS[6], J. YATES[7];
[1]Ophthalmology, UCLA, Los Angeles, CA; [2]Univ. of Washington, Seattle, WA; [3]Univ. of California, Berkeley, Berkeley, CA; [4]Psychiatry, UCLA Chapter, Los Angeles, CA; [5]Ctr. of

Visual Sci., Univ. of Rochester, Rochester, NY; [6]Dept. of Biol., Univ. of Maryland, Col. Park, College Park, MD; [7]Optometry, UC Berkeley, Berkeley, CA

Abstract: Neurons in visual cortex produce variable responses to repeated presentations of the same stimulus, and this variability is shared across neurons. The dominant interpretation treats this shared variability as internally generated, and a fundamental constraint on neural coding. Meanwhile, a separate literature has established that the eyes are never truly still during fixation, and that these fixational eye movements (FEMs) play a perceptual role in high-acuity vision. These two lines of work have remained largely disconnected. I will present evidence that they are, in fact, two sides of the same coin. Using high density electrophysiology recordings from primary visual cortex (V1) in marmosets combined with ultra-precise dual-Purkinje-image eye tracking, we decompose population variability into stimulus-locked, eye-movement-dependent, and residual components. We find that FEMs account for the majority of shared variability in central V1. After correcting for eye movements, Fano factors drop to sub-Poisson levels and pairwise noise correlations effectively vanish. The FEM-driven component is low-dimensional — consistent with two-dimensional shifts of the retinal image — and is embedded within stimulus-tuned population dimensions. These results suggest that much of what has been treated as neural noise in primate V1 is instead the sensory consequence of an ongoing active sampling strategy. I will discuss the implications for how we think about variability, correlations, and population codes in visual cortex.

Disclosures: D.P. Rowley: None. **R. Ressmeyer:** None. **T. Kothapalli:** None. **A. Huk:** None. **J.F. Mitchell:** None. **D.A. Butts:** None. **J. Yates:** None.

Poster

PSTR237: Neuroethology: Sensory Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR237.23/HH9

Topic: G.01. Neuroethology

Support: NTNU PES Grant 102750
The Kavli Foundation

Title: Using hibernation to uncover neural mechanisms of memory

Authors: *B. R. KANTER;
NTNU, Trondheim, Norway

Abstract: All animals use memories of their past to guide future behavior, exploiting opportunities while avoiding threats. Although much is known about the neural basis of memory, this knowledge comes from a limited number of species in a controlled lab setting. In diverse species and habitats that have so far remained inaccessible to neuroscientific study, memory mechanisms may substantially differ because brains are highly adaptive, inventing solutions to ecological challenges. To derive general principles of memory, we must leverage new tools and

animal models to move toward the naturalistic contexts in which brains evolved.
One extreme ecological challenge likely to shape memory circuits is hibernation - to survive food scarcity, thousands of species enter this state of profound metabolic suppression that lasts from a few hours to many weeks. Unlike sleep, during which neural activity helps to preserve memories, hibernation silences neural activity, potentially erasing memories and leaving animals at risk. Animals must remember where to find food and shelter to survive, and thus must have evolved adaptive neural mechanisms to protect memory.
Here, I present ongoing efforts to establish two new, complementary animal models for studying memory: 1) Peromyscus maniculatus (deer mice), which frequently enter short bouts of hibernation to conserve energy; and 2) Qrfp-iCre transgenic house mice, in which activating a subset of hypothalamic neurons mimics hibernation, thereby enabling precise temporal control. I will present preliminary data on inducing hibernation in the lab, using wireless telemetry to continuously record body temperature over many weeks, recording hippocampal activity at temperatures below 24C, designing an ethological daily memory task, and attempting to perform chronic high-density recordings in freely-moving Peromyscus mice.

Disclosures: B.R. Kanter: None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.01/HH10

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant U19NS128613
American Heart Association Grant 24PRE1201066
NIH Grant T32NS115667
NIH Grant T32GM108563
American Heart Association Grant 25PRE1371919
NIH Grant F31ES036154
Keck, W.M., Foundation Grant CRM0137656
NIH Grants R01AA031472
NIH Grants R01AA029403

Title: Coordinated norepinephrine and pyramidal neuron activity drives vascular dynamics during sleep and arousal

Authors: *M. HOSSAIN[1,2,3], M. R. WENKE[4,2,3,10], J. FLORES[4,2,5], A. SICHER[5,2], D. GREENAWALT[6,2], K. L. TURNER[11,7], N. A. CROWLEY[5,2,8,9], P. J. DREW[5,7,3,2,9];
[1]Biomed. Engin., Pennsylvania State Univ., State College, PA; [2]Penn State Neurosci. Inst., [3]Ctr. for Neural Engin., [4]Neurosci. Grad. Program, [5]Dept. of Biol., [6]Grad. Program in Mol. Cell. and Integrative Biosci., [7]Dept. of Engin. Sci. and Mechanics, [8]Dept. of Biomed. Engin., [9]Dept. of

Neurosurg., The Pennsylvania State Univ., University Park, PA; [10]Penn State Col. of Med., Hershey, PA; [11]Dept. of Biomed. Engin., Brown Univ., Providence, RI

Abstract: Cerebral blood volume (CBV) is dynamically regulated during both functional hyperemia and sleep-wake transitions. During sleep, cortical arteries undergo large spontaneous dilations and constrictions that exceed sensory-evoked functional hyperemia and are thought to facilitate cerebrospinal fluid movement and waste clearance. Although both cortical pyramidal neuron activity and neuromodulatory systems influence vascular dynamics, how these signals interact to regulate CBV remains poorly understood.To address this question, we used fiber photometry to measure CBV, norepinephrine (NE), acetylcholine (ACh), and pyramidal neuron calcium activity in the somatosensory whisker cortex of head-fixed mice across behavioral and sleep states. Sensory whisker stimulation evoked rapid increases in pyramidal neuron calcium activity and cortical ACh and NE levels, followed by an increase in CBV, followed by a post stimulus undershoot. Across sleep-wake states, sleep was characterized by reduced NE and ACh levels, increased CBV, and elevated pyramidal neuron calcium activity. Conversely, arousal from sleep triggered rapid increases in NE and ACh levels, vasoconstriction, and suppression of pyramidal neuron activity.Optogenetic activation of locus coeruleus (LC) noradrenergic neurons induced pupil dilation, suppressed pyramidal neuron activity, and reduced CBV. These effects were attenuated by adrenergic receptor antagonism, supporting a causal role for NE signaling in vascular tone.Mathematical modeling further demonstrated that NE levels and pyramidal neuron activity are jointly necessary and sufficient to predict CBV dynamics during sensory stimulation. The model fitted to sensory-evoked responses accurately predicted CBV changes during arousal-state transitions. Incorporating ACh into the model provided little or no additional explanatory power. Together, these findings support a model in which CBV is regulated by opposing noradrenergic vasoconstriction and pyramidal neuron activity-dependent vasodilation. During sleep, elevated CBV likely reflects reduced NE tone combined with increased pyramidal neuron activity, whereas awakening represents a high-NE state that suppresses pyramidal neuron activity and reduces CBV. In contrast, sensory stimulation produces a temporally dissociated relationship between NE and pyramidal neuron activity, resulting in modest functional hyperemia when pyramidal activity is greatest and subsequent post-stimulus vasoconstriction driven by delayed NE signaling.

Disclosures: M. Hossain: None. **M.R. Wenke:** None. **J. Flores:** None. **A. Sicher:** None. **D. Greenawalt:** None. **K.L. Turner:** None. **N.A. Crowley:** None. **P.J. Drew:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.02/HH11

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH 1R01NS138179
NIH R21NS142439
NIH Grant 1R01AG066645

Title: Single-cell transcriptomic profiling of hippocampal vascular cells reveals adaptation to neuronal activity

Authors: *G. PARK, N. WEIR, T. LONGDEN;
Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Electrical signaling between vascular cells is central to cerebral blood flow regulation, and we recently discovered a remarkable form of plasticity that tunes this process to precisely match blood flow to energy demands. Here, we found that capillary endothelial cells (ECs) adapt their electrical signaling to local neuronal activity by upregulating inwardly rectifying potassium (Kir) channels, which initiate and propagate hyperpolarization from capillaries to upstream arterioles. This adaptation augments vessel dilation during local increases in energy demand and preventing this vascular signaling plasticity (VSP) impaired learning—establishing VSP as important for brain energy homeostasis and neuronal function. However, what broader transcriptional adaptations accompany this Kir mechanism in ECs and mural cells (smooth muscle cells and pericytes), and what regulators drive them, remain unknown. We therefore used single-cell RNA sequencing to explore vascular transcriptional adaptation to a paradigm that increases neuronal activity in the hippocampus. Mice were housed in an enriched condition with a running wheel, toys, and a shelter dome, whereas control mice were housed with only minimal bedding. After 1 day, hippocampi were mechanically isolated. Each sample pooled 16 mice with both sexes equally represented, and vasculature cells were captured using CD31-coated magnetic beads. We obtained 16,000 ECs and 2,000 mural cells, classified along the arterial-venous axis into 3 EC subtypes and 5 mural subtypes. Differential gene expression analysis identified >100 upregulated and >200 downregulated genes in ECs and >20 upregulated and >20 downregulated genes in mural cells. Gene set enrichment analysis revealed upregulation of regulatory secretory pathway and histone demethylase activity pathways, while ribosomal and immune response pathways were downregulated. Weighted Gene Co-expression Network analysis (hdWGCNA) showed enrichment of gene modules related to blood vessel development, alongside downregulation of modules associated with cytoplasmic translation and inflammatory response. Gene regulatory network analysis (DoRothEA) further identified the transcription factors *Tal1*, *Gata3*, and *Gata2* as more active in ECs during enrichment. Together, these findings move beyond the known Kir adaptation of VSP to map a broader transcriptional program through which vascular cells respond to elevated energy demand. The candidate genes and regulators identified provide a foundation for dissecting VSP in detail and for developing strategies to restore or preserve neurovascular coupling in brain disorders with a vascular component.

Disclosures: G. Park: None. **N. Weir:** None. **T. Longden:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.03/HH12

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NINDS Grant 1R01NS138179
NIA Grant 1R01AG066645
NINDS Grant R21NS142439

Title: Elucidating the mechanisms of capillary-level neurovascular coupling via control of thin-strand pericyte Ca^{2+} activity

Authors: *S. JU, T. A. LONGDEN;
Pharmacol. and Physiol., Univ. of Maryland, Sch. of Med., Baltimore, MD

Abstract: Pericytes occupy every branch of the cerebral capillary bed and play key roles in regulating blood flow, controlling the blood-brain barrier, and orchestrating angiogenesis. The "thin-strand" subtype of pericytes (TSPs), found in the deepest reaches of the capillary bed, plays a central role in neurovascular coupling (NVC)—a suite of mechanisms that translates increased neuronal activity into augmented local blood flow. We previously showed that TSPs can initiate capillary-to-arteriole electrical signaling via K_{ATP} channel activation and subsequently identified a signaling pathway within TSPs that regulates this transmission in the form of a voltage-dependent calcium (Ca^{2+}) channel-endoplasmic reticulum-Ca^{2+}-activated chloride channel (VDCC-ER-CaCC) module, which opposes vasodilatory signals via depolarization of local capillaries. During neuronal activation, Ca^{2+} activity in TSPs is dramatically suppressed to turn off CaCCs and create a permissive environment for hyperpolarizing electrical signaling. However, the mechanism underlying this aspect of NVC remains poorly understood, and little is known about the endogenous molecular players modulating basal Ca^{2+} activity in TSPs. Identifying these mechanisms is therefore crucial to reveal new layers of neurovascular control, the breakdown of which may inform potential therapeutic and preventative targets in neurodegenerative diseases with vascular involvement. To explore this, we used *ex vivo* Ca^{2+} imaging via confocal microscopy to visualize cytosolic Ca^{2+} activity in TSPs in acute cortical slices from PDGFRβ-Salsa6f mice, expressing a ratiometric Ca^{2+} biosensor combining GCaMP6f with TdTomato labeling in pericytes and smooth muscle cells. Responses to a range of NVC mediators were assessed via Ca^{2+} activity metrics obtained using the Activity Quantification and Analysis (AQuA2) tool. This analysis revealed a central role for $G\alpha_q$-coupled receptor signaling in TSP Ca^{2+} dynamics, which may play an important role in vascular regulation. Future experiments will build on these data and extend to *in vivo* pharmacology and imaging studies using cranial window surgeries, multiphoton imaging, and patch clamp electrophysiology.

Disclosures: S. Ju: None. **T.A. Longden:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.04/HH13

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant HL007284
UVA Brain Institute Postdoctoral Fellowship
Owen's Family Foundation
NIH Grant NS122782
NIH Grant NS119243
AHA Grant 25POST1376070

Title: The Role of Microglia and Astrocyte Cyclooxygenase-1 in the Modulation of Basal Capillary Tone in vivo

Authors: *W. A. MILLS III, U. B. EYO;
Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Microglia and border associated macrophages have been implicated in hypercapnia, but it is unknown which myeloid cell modulates which vessel type. Previously, we documented in mice myeloid cell association with the brain vasculature but did not distinguish their localization along the vascular tree. Using molecular approaches to distinguish microglia and perivascular macrophages, we show that microglia are the only myeloid cells associating with capillaries. To determine if loss of microglia is sufficient to reduce capillary tone, we employ global and focal ablations and find significant reductions in capillary diameter and red blood cell flux, suggesting vasodilatory regulation by microglia. Cyclooxygenase-1 (COX1), an enzyme with known vasodilatory action, is predominantly expressed by microglia. To determine the necessity of microglial COX1 in regulating cerebral basal capillary tone in vivo, we perform genetic ablation and find a significant reduction in capillary flux and diameter. We do not observe this following genetic ablation of astrocyte COX1. Together, this study using male mouse models reveals a role for microglial COX1 in maintaining basal capillary tone in vivo.

Disclosures: W.A. Mills III: None. **U.B. Eyo:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.05/HH14

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant AG079336
NIH Grant AG057842
NIH Grant AG094068
AHA Grant 25PRE1365157
Augusta University startup TRIBA

Title: Impaired Cerebrospinal Fluid Drainage is Associated with Cognitive Deficits and Cerebrovascular Dysfunction in Healthy SD Rats

Authors: *G. MORGAN[1], R. DONG[2], Y. HANSCOM-TROFY[2], A. GREGORY[3], F. FAN[4]; [2]Physiol., [1]Augusta Univ., Augusta, GA; [3]Physiol., Augusta university, Beech island, GA; [4]Physiol., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Glymphatic impairments and vascular abnormalities emerge as early hallmarks in the pathogenesis of Alzheimer's disease (AD). Clinical investigations have revealed that surgical interventions facilitating glymphatic fluid drainage improve cognitive performance in AD patients within just one week. While mainstream theories attribute these rapid clinical improvements to enhanced cerebrospinal fluid (CSF) circulation and glymphatic clearance of amyloid-β (Aβ) and tau, such acute clearance mechanisms alone cannot account for these immediate cognitive benefits. We hypothesize that facilitating glymphatic fluid drainage provides dual benefits in AD by promoting vascular protection and facilitating Aβ clearance. This study was designed to explore whether blocked CSF drainage and impaired glymphatic outflow may alter cognitive status and cerebrovascular activity in healthy Sprague-Dawley (SD) rats. All experiments were conducted using 24-week-old SD rats. Animals were anesthetized with 3% isoflurane, and a surgical procedure, validated in pilot studies by Evans Blue dye accumulation only upstream of the ligation site following intranasal instillation, was performed to obstruct bilateral cervical efferent lymphatic drainage. Cognitive function was assessed using the Novel Object Recognition test at 1 week and 4 weeks following surgery, and cerebral vascular function was examined using whisker-stimulated functional hyperemia and the myogenic response of the middle cerebral artery (MCA). Compared with sham-operated controls, experimental rats exhibited a nonsignificant trend toward cognitive decline at one week post-intervention, which progressed to significant cognitive impairment by week four. Moreover, the myogenic response of the MCA and whisker-evoked functional hyperemia were significantly diminished in association with disrupted glymphatic drainage. These findings support the hypothesis that enhancing glymphatic fluid drainage may exert dual benefits for AD management by protecting cerebrovascular function and accelerating Aβ clearance.

Disclosures: G. Morgan: None. **R. Dong:** None. **Y. Hanscom-Trofy:** None. **A. Gregory:** None. **F. Fan:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.06/HH15

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: FAPESP: 2025/03278-7
2025-05255-4; CNPq: 408542/2025-0

Title: Modulation of cardiovascular responses to reduced cerebral blood flow by the oxygen levels in the brain

Authors: *L. RODRIGUES MENDES[1], I. P. LEIRÃO[3], F. CAMPOS DE MEDEIROS[2], D. S. COLOMBARI[4], E. COLOMBARI[5], D. ZOCCAL[3];
[1]Dept. of Physiol. and Pathology, São Paulo State Univ. (UNESP), São Paulo, Brazil; [2]Physiol. & Pathology, São Paulo State Univ. (UNESP), Araraquara, Brazil; [3]Dept. of Physiol. and Pathology, Sch. of Dent. (FOAr), Sao Paulo State Univ. (UNESP), Araraquara, Brazil; [4]Physiol. & Pathology, UNESP Sch. of Dent., Araraquara, Brazil; [5]Physiol. & Pathology, Sch. of Dent. of Araraquara - UNESP, Araraquara, Brazil

Abstract: Increases in intracranial pressure (ICP) reduce cerebral blood flow (CBF) and oxygen (O_2) delivery to the brain. These changes are detected by specialized cells in the brain that monitor cerebral perfusion or tissue oxygen levels (PtO_2), triggering reflex stimulation of the sympathetic nervous system and respiratory network. It remains unclear whether reduced CBF or brain hypoxia is the primary stimulus for cardiorespiratory responses to increased ICP. To dissect this question, we examined how different inspired oxygen levels modulate CBF and cardiorespiratory responses to increased ICP. Male Sprague-Dawley Holtzman rats anesthetized with urethane (1.2 g/kg, i.v.) were instrumented for continuous recording of mean arterial pressure (MAP), diaphragmatic activity (DIA), ICP (measured in the lateral ventricle), CBF, and PtO_2, and were exposed to different levels of inspired O_2 (21%, 50% or 100% O_2 for 10 min). Increases in ICP were induced by altering the height of a water column connected to the contralateral lateral ventricle. Data (mean±SD) were analyzed using two-way ANOVA, followed by Bonferroni post hoc test. ICP increases of 30-40 mmHg reduced CBF by 35-40%, with the magnitude not differing across inspired O_2 levels. This response was accompanied by reductions in PtO_2 in the animals breathing 21 and 50% O_2 (Δ: -32±12 and 22±12%, $P<0.05$; n=7); but not 100% O_2 (Δ: 9±11%, n=8). In all groups, ICP increase caused significant increases in MAP; however, the magnitude of this response was higher in animals breathing 21% O_2 (Δ: 13±8 mmHg, n=14, P=0.0231) compared to animals breathing hyperoxic mixtures (Δ: 6±6 and 7±6 mmHg, 50 and 100% O_2, n=19 and 8). DIA amplitude and respiratory frequency also increased as ICP changed; however, the magnitude of these responses did not differ across different O_2 levels (n=11-14). These results demonstrate that hyperoxia can preserve cerebral tissue oxygenation during hypoperfusion induced by increased ICP and modulate the magnitude of the reflex increase in MAP. However, maintaining brain oxygenation neither abolishes the pressor response nor attenuates the increase in the respiratory response, suggesting that reductions in CBF are the primary stimulus activating the sympathetic and respiratory systems.

Disclosures: L. Rodrigues Mendes: None. **I.P. Leirão:** None. **F. Campos de Medeiros:** None. **D.S. Colombari:** None. **E. Colombari:** None. **D. Zoccal:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.07/HH16

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: TSNRP

Title: Non-invasive capacitive sensing system for cardiorespiratory and intracranial pressure monitoring in a rodent model

Authors: *K. H. CHOI;
Uniformed Services Univ., Bethesda, MD

Abstract: Continuous and non-invasive monitoring of cardiorespiratory and intracranial pressure (ICP) data is crucial for neurocritical care and predicting outcomes following brain injury. However, currently available technologies often lack the necessary sensitivity, noninvasiveness, and real-time tracking capabilities. To bridge this gap, a non-invasive capacitive sensing system (NCSS) was developed for cardiorespiratory and ICP monitoring, validating its performance against well-established pulse oximetry in a rodent model. Young adult male Sprague-Dawley rats were monitored under inhalation isoflurane anesthesia while independent variables, such as anesthesia concentration (1-3%) and the Valsalva maneuver (abdominal-thoracic-cranial link), were tested. Vital signs—including heart rate (HR), breath rate (BR), pulse distention (μm), blood oxygen saturation (SpO_2), and core body temperature—were simultaneously monitored alongside non-invasive brain capacitance signals. Increasing isoflurane concentration reduced HR and BR while increasing pulse distention. The brain capacitance also altered following anesthetic changes, exhibiting pulse waveforms that resolved into low-frequency respiratory and high frequency heartbeat signals. Using MATLAB for signal processing and frequency-domain analysis, quantifiable HR and BR were successfully derived from the capacitance signals, demonstrating statistically significant correlations with the pulse oximetry data. Furthermore, the Valsalva maneuver induced brain region-specific increases in capacitance signals following abdominal compression. These results demonstrate that the NCSS can accurately estimate cardiorespiratory and ICP metrics in animal models, establishing a viable method for non-invasive ICP monitoring in cardiovascular research, neuroscience, and clinical practice.

Disclosures: K.H. Choi: None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.08/HH17

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH grant R61NS137365

Title: Bi-directional control of brain capillary diameter using pericyte chemogenetics

Authors: T. MCGILLIS[1], S. STAMENKOVIC[2], V. STAMENKOVIC[3], S. NAIR[4], Z. ZHAO[5], ***A. Y. SHIH**[3];
[1]Ctr. for Developmental Biol. and Regenerative Med., Seattle Children's Res. Inst., Kent, WA; [2]Ctr. for Developmental Biol. and Regenerative Med., [3]Seattle Children's Res. Inst., Seattle, WA; [4]Stanford OHS, Stanford Online High Sch., Seattle, WA; [5]Biomed. Informatics and Genomics, Tulane Univ., New Orlean, LA

Abstract: Capillaries represent more than 90% of the brain's vascular length and function as a vast distribution network for blood throughout the brain. Altered capillary blood flow is implicated in numerous disease conditions; however, there are currently no models that enable specific modulation of brain capillaries in vivo to directly examine their roles in pathology. To address this gap, we developed two novel mouse models for chemogenetic stimulation of capillary pericytes that line capillaries throughout the central nervous system. Expression of the chemogenetic actuators Gq-DREADD or Gs-DREADD was driven by the CNS pericyte-specific promoter Atp13a5. These mice were designated Pericyte-Gq-DREADD and Pericyte-Gs-DREADD. The ability to modulate capillary diameter and blood cell flow was demonstrated in the somatosensory cortex and callosal white matter using in vivo deep two-photon imaging. Activation of Pericyte-Gq-DREADD mice through acute administration of the potent blood-brain barrier-permeant DREADD agonist deschloroclozapine (DCZ) resulted in robust capillary constriction, producing an average 15% reduction in baseline diameter and a 40% reduction in red blood cell flux, with complete flow stalls occurring in many cases. We further show that this constriction can be reversed by the clinically used Rho kinase inhibitor Fasudil, suggesting that pericyte contraction can be alleviated pharmacologically and that Pericyte-Gq-DREADD mice may serve as a useful therapeutic test bed for drugs that relax pericytes. Conversely, acute Gs-DREADD activation produced strong capillary dilation and increased cortical blood flow. We further show that capillaries in the callosal white matter of Pericyte-Gs-DREADD mice can dilate and increase white matter perfusion, enabling experiments to test whether enhanced white matter perfusion can rescue white matter pathology associated with aging and other disease conditions. Overall, these novel mouse lines open the door to new studies of brain capillary perfusion and the physiology underlying blood flow regulation within the brain's capillary network.

Disclosures: T. McGillis: None. **S. Stamenkovic:** None. **V. Stamenkovic:** None. **S. Nair:** None. **Z. Zhao:** None. **A.Y. Shih:** F. Consulting Fees (e.g., advisory boards); Advisory board member for Stream Biomedical Inc..

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.09/HH18

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Grant-in-Aid for Scientific Research (KAKENHI) (26462156).

Title: Vasorelaxation induced by beta-adrenoreceptor agonist in cerebral arteries with experimental SAH model.

Authors: *T. MURATA;
Minaminagano Med. Ctr. Shinonoi Gen. Hosp., Nagano, Japan

Abstract: Delayed cerebral ischemia (DCI) following subarachnoid hemorrhage (SAH), which results in an unfavorable clinical outcome, is thought to be caused by the combined effects of delayed cerebral vasospasm, arteriolar constriction and microthrombosis, cortical spreading ischemia, and processes triggered by early brain injury. Delayed cerebral vasospasm is one of the major causes of DCI, however, its pathophysiological mechanisms still remain unresolved despite progress in experimental and human investigations, thus limiting the number of available effective therapies. Beta-adrenoreceptor agonist, such as Ritodrine Hydrochloride, is a well-known vascular relaxant which treated in patients with threatened premature delivery. This study was therefore conducted to clarify that the beta-adrenoreceptor agonist induce vasorelaxation in cerebral artery tone, and to investigate the messenger RNAs (mRNAs) expression of beta-adrenoreceptor on rabbit, dog and human basilar artery, and also to investigate the beta-adrenoreceptor agonist induced- vasorelaxation effect the cerebral vasospasm in dog experimental SAH model. In this study, rings of male rabbit basilar arteries were suspended in organ bath and measured with the beta-adrenoreceptor agonist as Ritodrine Hydrochloride and Clenbuterol Hydrochloride. Selective beta-adrenoreceptor agonists were also tested. SAH was induced twice using a venous blood injection method into the cisterna magna of male dog under general anesthesia. The beta-adrenoreceptor agonist, Ritodrine Hydrochloride and Clenbuterol Hydrochloride, dose-dependently relaxed on KCl-induced contraction of rabbit basilar artery. The selective beta-1-adrenoreceptor agonist, Dobutamine Hydrochloride, dose-dependently relaxed on KCl-induced contraction of rabbit basilar artery. Neither the selective beta-2-adrenoreceptor agonist as Procaterol Hydrochloride nor the selective beta-3-adrenoreceptor agonist as CL 316,234 relaxed on KCl-induced contraction of rabbit basilar artery. The mRNAs expression of beta-1- and beta-2-adrenoreceptor were detected on rabbit, dog and human basilar artery, but beta-3-adrenoreceptor were not on these basilar arteries. Cerebral vasospasm of basilar artery in dog experimental SAH model was confirmed by cerebral angiography on 4 days after injection. In conclusion, the beta-adrenoreceptor agonist dose-dependently relaxed on rabbit basilar artery, and this vasorelaxation may be associated via the beta-1-adrenoreceptor. These results provide a background to develop in treatment against delayed cerebral ischemia or vasospasm following SAH.

Disclosures: T. Murata: None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.10/HH19

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Fondation Leducq 22CVD0
R01 NS063226
RF1 MH114276
Simons Collaboration on the Global Brain 542991
NSF GRFP
St Jude Children's Research Hospital

Title: Disambiguating normal neurovascular coupling from vasomotion using wide-field optical mapping in mice.

Authors: *A. BISHT[1], L. XU[1], C. FREEMAN[1], W. LI[1], E. M. HILLMAN[1,2];
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Abstract: Hemodynamic fluctuations are an important feature of normal cerebral hemodynamics. In the healthy rodent brain, spatiotemporal cortical hemodynamics can be predicted by temporally smoothing real-time fluctuations of neural activity, suggesting that real-time hemodynamics reflect a direct neurovascular coupling between neuronal activity and perfusion. Isolated arterioles, and vessels within a number of tissues including the brain, can also exhibit strongly sinusoidal oscillations in diameter and flow, often termed vasomotion. With a characteristic 0.1-0.2 Hz period, these oscillations can be evoked by a range of intrinsic or extrinsic factors and are believed to arise primarily from destabilized myogenic mechanisms entering into an oscillatory feedback loop. Nevertheless, some studies of 'resting-state' fluctuations in the brain claim that cortical hemodynamics represent an entrainment of vasomotion oscillations. Here, we employed widefield optical mapping (WFOM), that allows simultaneous cortex-wide imaging of neural activity through fluorescence imaging in mice expressing jRGECO1a in neurons. Simultaneous hemodynamic imaging was achieved through diffuse reflectance-based estimation of changes in oxyhemoglobin (ΔHbO), deoxyhemoglobin (ΔHbR), and total hemoglobin (ΔHbT). Resting state and bilateral whisker stimulus evoked (1 s and 5 s long stimulus) responses were collected before and after administration of L-NAME (~10-20 mg/ml, 75 mg/kg) which is a nitric oxide (NO) inhibitor well documented to evoke vasomotion oscillations in mice. Spectral analysis comparing neuronal and hemodynamic data across the cortex confirm that under normal conditions, HbT signals appear low-pass filtered at around 0.2 Hz, representing the smoothing effect of neurovascular coupling. After L-NAME, a prominent oscillatory component between ~0.1-0.2 Hz representing vasomotion was significantly higher. In contrast, spectral analysis of simultaneously acquired neuronal calcium data was relatively consistent between pre- and post- L-NAME administration, confirming that evoked vasomotion oscillations are an independent and aberrant feature of the cortical vasculature, and do not reflect a change in underlying neuronal activity, nor a state of normal neurovascular coupling. Building on mathematical models that more accurately predict neurovascular coupling as a combination of 'slow' and 'fast' components, we explore the mechanistic basis of oscillatory behaviors within this system. Our results point to the role of NO in slower coupling mechanisms that serve to stabilize the vasculature during normal neurovascular coupling.

Disclosures: A. Bisht: None. **L. Xu:** None. **C. Freeman:** None. **W. Li:** None. **E.M. Hillman:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.11/HH20

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant U19NS128613
NIH Grant T32NS115667
NIH Grant R01NS078168
NIH Grant R01NS101353

Title: Norepinephrine and Cerebral Arteriole Dynamics in Sleep-Deprived Mice

Authors: *M. WENKE[1,2,3,7], M. HOSSAIN[3,4], P. J. DREW[2,3,4,5,6];
[2]Pennsylvania State Neurosci. Inst., [3]Ctr. for Neural Engin., [4]Biomed. Engin., [5]Engin. Sci. and Mechanics, [6]Biol. and Neurosurg., [1]Pennsylvania State Univ., State College, PA; [7]Pennsylvania State Col. of Med., Hershey, PA

Abstract: During sleep, cerebral arteries dilate with periodic pulsations that are thought to drive cerebrospinal fluid flow and promote waste clearance from the brain. Norepinephrine (NE) release from cortical axonal projections originating from the locus coeruleus (LC) can drive vasoconstriction and arousal from sleep. LC hyperexcitability is a hallmark of many neurologic conditions, including chronic sleep insufficiency. Sleep deprivation increases sleep drive, but it also increases sleep fragmentation, correlating with higher magnitude and frequency of NE release from the LC. However, the effect of sleep deprivation on cortical NE and arterial dynamics are unknown.
We used two-photon imaging to observe cortical NE release alongside arterial diameter in the somatosensory cortex of head-fixed C57BL/6J mice as they sleep. We visualized local NE tone around penetrating arterioles through a thinned-skull window. We monitored non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states using electrocorticography, electromyography, pupillometry, and whisker movement. Our results show that during undisturbed sleep, NE around penetrating arterioles was highest during wakefulness, decreased during NREM accompanied with vasodilation, and was lowest during REM sleep. Immediately prior to arousal from sleep, local NE levels rapidly increased back to waking baseline levels, followed by vasoconstriction. Sleep deprivation promoted larger arteriole pulsations, and it increased NE transients and infraslow oscillation. Administration of prazosin, an alpha-1 adrenergic receptor antagonist, reduced microarousals and increased arterial pulsations while reducing NE spiking. Prazosin administration decoupled arterial pulsations from NE activity. Together these experiments suggest that increased NE dynamics after sleep deprivation could contribute to increased arteriolar pulsatility throughout subsequent NREM sleep.

Disclosures: M. Wenke: None. **M. Hossain:** None. **P.J. Drew:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.12/HH21

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01NS140868
NIH P20GM135007
NIH R01NS128963

Title: Kir2.1-mediated vasodilatory signaling in the thalamus

Authors: N. C. STINE, G. C. WELLMAN, ***M. KOIDE**;
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Abstract: As the brain has limited energy reserves, it requires a continual and adequate delivery of oxygen and nutrients to maintain function. These requisites are delivered via cerebral blood flow (CBF); thus, increased CBF occurs in active brain regions commensurate with enhanced metabolic demands. This CBF increase in response to focal neuronal activation is called functional hyperemia and is mediated by intercellular signaling termed neurovascular coupling. Our previous research found that capillaries, the smallest and most abundant vasculature in the brain, play a key role in neurovascular coupling. Strong inwardly rectifying Kir2.1 potassium channels in capillary endothelial cells (ECs) sense neuronal activation via modestly elevated perivascular K^+, followed by Kir2.1 channel activation, which initiates a vasodilatory hyperpolarizing signal. The vasodilatory signal propagates and leads to upstream arteriolar dilation, resulting in enhanced CBF at the site of active neurons. These findings were demonstrated in the somatosensory cortex, the most studied and well-established region of the brain in functional hyperemia research. However, neurovascular coupling mechanism(s) remain unclear in subcortical brain regions, including the thalamus. Here, we explored Kir2.1-mediated vasodilatory signaling in the thalamus, a critical brain region linking sensory, cognitive, emotional, and behavioral responses. Using conventional whole-cell patch-clamp electrophysiology, Kir2.1 currents were measured in freshly isolated thalamic capillary ECs. Kir2.1-mediated vasodilatory responses were evaluated in capillary-arteriole continuum (CaPA) preparations from the thalamus. We found Ba^{2+}-sensitive inward currents (i.e., Kir currents) in thalamic capillary ECs at a current density comparable to that in cortical capillary ECs. Further, as with cortical CaPA preparations, capillary stimulation with 10 mM K^+, which mimic focal neuronal activation, induced robust vasodilation in upstream thalamic arterioles. These data demonstrate the functional presence of Kir2.1-mediated capillary-to-arteriole vasodilatory signaling in the thalamus. Future studies will elucidate the role of Kir2.1-mediated vasodilatory signaling in neurovascular coupling in the thalamus and its contribution to vascular dementia caused by aging and cerebral small vessel diseases.

Disclosures: N.C. Stine: None. **G.C. Wellman:** None. **M. Koide:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.13/HH22

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NINDS RF1NS116450
NIA 1R01AG092661

Title: Novel metric of cerebral blood flow heterogeneity exposes regional drops in capillary perfusion with aging

Authors: *Y. SHEN[1], Y. ZHAO[1], H. FUKUDA[2], A. VAZQUEZ[2], B. IORDANOVA[1];
[1]Dept of Bioengineering, [2]Dept of Radiology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cerebral blood flow governs oxygen and glucose delivery, playing an essential role in brain health. Mean transit time (MTT) and capillary transit-time heterogeneity (CTH) are established neuroimaging metrics used to evaluate cerebral perfusion. Crucially, aberrant changes in MTT and CTH have been linked to cognitive decline, and variance in CTH affects oxygen extraction fraction. However, how MTT and CTH evolve in healthy ageing across the sexes remains unclear. In this study we develop novel metrics to quantify cerebral blood flow heterogeneity in wide-field optical imaging. We used 49 B6C3F1/J mice (24 females, 25 males) in a cross-sectional cohort 2 to 14 months. The mice had tail vein cannulation and cranial window installation under urethane. Wide-field fluorescence imaging captured the transit of an intravenous fluorescent bolus through the vascular tree. Vessels were segmented, and arteries and veins were differentiated based on arrival times. MTT was computed as the peak-to-peak time difference between arterial and venous curves. The transport function between arteries and veins was fitted to a gamma distribution, with CTH defined as its standard deviation. Furthermore, we evaluated the pixelwise arrival time within the tissue parenchyma. The full width at half maximum of the arrival time histogram, termed spatial heterogeneity, was extracted to capture regional perfusion. We used 4μm intravenous microspheres to evaluate the vascular resilience across age and sex. Linear mixed-effects model and Davies test were used to determine parameter relationships. At baseline, no sex or age effects were observed for MTT and CTH. However, the Davies test showed a significant age-dependent breakpoint in the novel metric of spatial heterogeneity for the males ($p = 0.038$), with slope transition occurring at 8.15 months. Following microvascular occlusion with microspheres, spatial heterogeneity significantly increased in both sexes ($p = 0.049$). The linear mixed effect model revealed a significant sex-injection interaction in MTT ($p = 0.009$). Traditional vascular heterogeneity metrics lack the sensitivity to resolve regional microvascular alterations. The novel metric of spatial heterogeneity resolves sex-specific microvascular trajectories, enabling translational insights into vascular aging.

Disclosures: Y. Shen: None. **Y. Zhao:** None. **H. Fukuda:** None. **A. Vazquez:** None. **B. Iordanova:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

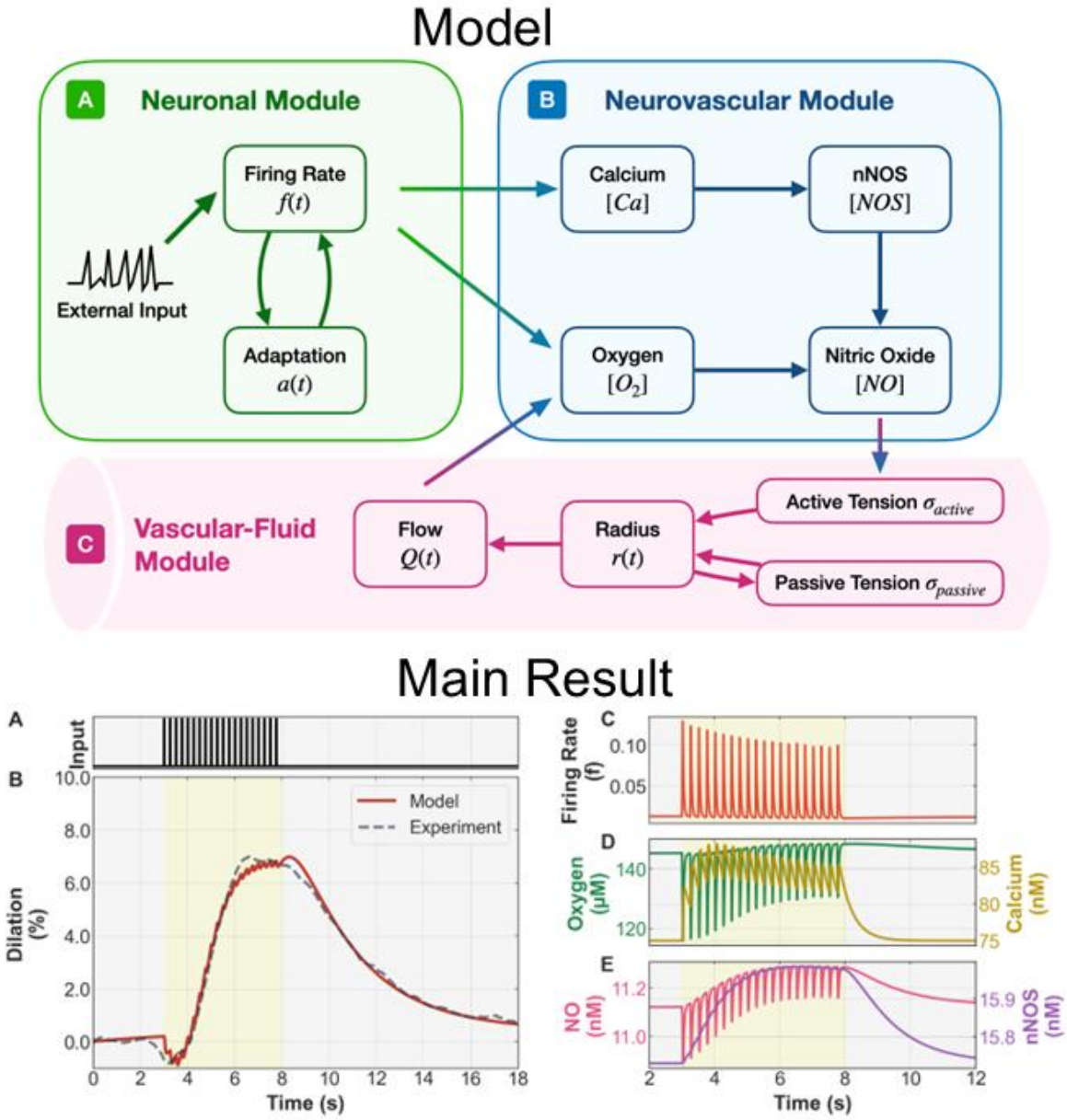
Program #/Poster #: PSTR238.14/HH23

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: A compact model for neuronal regulation of arteriolar blood flow in the mouse brain

Authors: *G. SUN, C. S. PESKIN;
Courant Inst. of Mathematical Sci., New York Univ., New York, NY

Abstract: The brain continuously adjusts local blood flow to match the metabolic demands of its neurons, a process termed functional hyperemia. This important process spans across multiple cell types and environments, making its underlying mechanism difficult to elucidate. Here, we introduce an ordinary differential equation model that couples three dynamical systems: adaptive neuronal firing-rate dynamics, neurovascular coupling, and vascular wall mechanics. Fitting the model to published mouse barrel-cortex arteriole data during whisker stimulation reproduces the observed dilation waveform, including a transient sub-baseline constriction followed by delayed dilation. Stimulus sweeps predict a nonlinear, non-monotonic dependence of peak dilation on neuronal stimulus frequency and duration, reflecting the interaction between adaptation, oxygen demand, and delayed NO signaling. Finally, variations in arteriole stiffness expose a ridge of maximal dilation responsiveness, suggesting that functional hyperemia depends on a tuned mechanical operating regime rather than on stiffness alone. These findings align with the current experimental observations, and our model offers testable predictions for the underlying mechanism.



Disclosures: G. Sun: None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.15/HH24

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Intramural Research Program of the National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD. Grant #: NS009456-01

Title: Volumetric spatiotemporal characterization of brain capillary endothelial calcium signals

Authors: *J. B. GARFINKEL[1], A. ROEHRKASSE[1], M. EIDEN[1], S. M. HOOPER[2], A. MUGHAL[1];
[1]Neurovascular Res. Unit, Stroke Br., Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [2]Office of AI Res., Natl. Heart Lung and Blood Inst., Bethesda, MD

Abstract: Capillary endothelial cell (cEC) calcium (Ca^{2+}) signaling plays a critical role in controlling local blood flow in the brain. However, most *in vivo* characterization of cECs Ca^{2+} activity has relied on single-plane imaging, limiting our ability to capture the full spatiotemporal extent of these signals. Here we present an image analysis pipeline to identify cECs Ca^{2+} activity in four dimensions and quantify event characteristics. The analysis pipeline is comprised of three main stages: image preprocessing, vessel structure identification, and event detection. In preprocessing, images were first denoised using a deep learning model, then deconvolved to reduce blurring. Next, plasma signals were used to segment the vessel lumen in three dimensions (3D). After dilation, the vessel mask was used to constrain subsequent event detection to regions where cEC Ca^{2+} activity could occur. We then employed an event identification and segmentation algorithm to identify Ca^{2+} activity.To test this pipeline, we used two-photon 3D over time (4D) images of head-fixed awake mice. These mice were genetically encoded with GCaMP8 in the endothelial cells with VE-cadherin (*Cdh5*) promoter to visualize Ca^{2+} transients. We injected these mice with a plasma marker; Texas Red-dextran (250 KDa) for identification of the brain vasculature.Validation of the signal identification pipeline against manually annotated Ca^{2+} events yielded an 83% hit rate. These validated activity maps then enabled downstream characterization of events, including measurements of rise and decay half-time (and , respectively), maximum spatial length, and extension speed. For analysis, we restricted events to those which extended beyond their initial length and do not start on the first frame or end on the last frame. Our analysis of multiple datasets from 10 mice shows the median event was 2.55 sec (min: 0.05 sec, max: 21.85 sec) and 2.45 sec (min: 0.06 sec, max: 21.80 sec) for . Event spread is variable, with a median spatial length of 15.97 μm and median linear extension speed of approximately 1.33 $\mu m \bullet sec^{-1}$ (min: 0.02 $\mu m \bullet sec^{-1}$, max: 80.51 $\mu m \bullet sec^{-1}$). Together, these results describe a validated 4D analysis pipeline for identifying cEC Ca^{2+} activity in volumetric two-photon data. Across detected events, we observed a wide spectrum of event characteristics, from brief, localized transients to spatially expansive, slowly decaying signals. This characterization enables event-level filtering and targeted spatiotemporal analysis that can inform the interpretation of cECs Ca^{2+} dynamics in large field-of-view volumetric imaging.

Disclosures: J.B. Garfinkel: None. **A. Roehrkasse:** None. **M. Eiden:** None. **S.M. Hooper:** None. **A. Mughal:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.16/HH25

Topic: D.03. Stroke

Support: National Science Foundation of China (No. 82371486)

Title: Multifaceted cerebrovascular atlases of rhesus monkey from TOF-MRA

Authors: *Y. CUI[1], J. GAO[2], Y. ZHANG[1], J. LIU[1], T. JIANG[1], M. SONG[1], Z. CHEN[3], S. YU[1]; [1]Inst. of Automation Chinese Acad. of Sci., Beijing, China; [2]Beijing Normal Univ., Beijing, China; [3]Capital Med. Univ., Beijing, China

Abstract: Mapping the vascular organization of the brain is fundamental to understanding the mechanisms underlying brain function and to developing therapeutics for neurovascular and neurodegenerative disorders. The rhesus monkey (*Macaca mulatta*) is an indispensable experimental model that shares extensive genetic, neuroanatomical, and behavioral characteristics with humans. Yet vascular atlases characterizing the distribution and morphology of the cerebral vasculature based on in vivo neuroimaging remain absent in the primate brain. Here, we present a comprehensive collection of statistical atlases encompassing the whole brain and the Circle of Willis of rhesus monkeys, constructed from multicenter time-of-flight magnetic resonance angiography (TOF-MRA) data. These multifaceted brain maps characterize not only vascular probability but also detailed morphological and geometric properties, including vessel diameter, tissue-to-vessel distance, stenosis, tortuosity, deviation, and angulation. The resulting normative macaque atlases provide a population-level reference framework for detecting disease-related vascular deviations through z-score mapping, as demonstrated in a non-human primate model of the amyloid pathology. Specifically, six male monkeys (9.8±3.9 years; 7.8±2.9 kg) received bilateral hippocampal injections of an adeno-associated virus encoding the double Swedish mutation of amyloid precursor protein (AAV-APP k595n/m596l), while six age-matched male monkeys (11 ± 4.5 years; 8.1 ± 1.6 kg) served as controls. Notably, posterior cerebral arteries of AAV-injected monkeys exhibited significant luminal narrowing relative to controls at five-month follow-up, suggesting that exogenous amyloid protein administration in the hippocampus may adversely remodel the morphology of the posterior cerebral artery, which is the primary and most consistent arterial source perfusing the hippocampal formation through its distinct branches. These findings demonstrate that the normative Circle of Willis atlas enables precise detection and quantification of individual-level z-score deviations, establishing it as a powerful and sensitive translational tool for investigating cerebrovascular pathology in nonhuman primate models of neuropsychiatric and neurodegenerative diseases. Collectively, the present study establishes a spatially referenced framework for the vasculature organization of the primate brain, offering a valuable resource for integrating and interpreting neuroimaging data, facilitating cross-species comparisons, and advancing translational neuroscience and medicine.

Disclosures: Y. Cui: None. **J. Gao:** None. **Y. Zhang:** None. **J. Liu:** None. **T. Jiang:** None. **M. Song:** None. **Z. chen:** None. **S. Yu:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.17/HH26

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: F32NS134617
T32MH126388

Title: Endothelial Network States Gate Rapid, Behaviorally Timed Increases in Blood-Brain Barrier Permeability

Authors: *K. L. TURNER, S. FEKIR, S. J. SCOTT, C. JOHNSON, C. I. MOORE;
Brown Univ., Providence, RI

Abstract: The blood-brain barrier (BBB) is classically viewed as static and restrictive. Yet, forebrain circuits driving behavior could benefit from dynamic, localized access to the contents of the vascular system, a high-dimensional source of body-state information ideal for guiding action and learning. Using two-photon imaging of an intravascular tracer (70 kDa Rhodamine B) in primary somatosensory neocortex (SI), we previously identified 'Plume Events': brief, spatially restricted increases in BBB permeability that emerge from pial and penetrating arterioles independent of vasodilation. Plume Events are timed to behaviorally relevant moments. In Pavlovian conditioning, they occur immediately preceding and ~1s after Reward. Following Instrumental conditioning, these Plume Events are also found across mice, and a new 'type,' immediately following Sensory Cue, emerges (N = 3 cohorts, 3-4 mice each, each behavioral one-hour session contained several hundred events). The endothelial cells (EC) lining these vessels form a key part of the BBB and are uniquely positioned to respond to both luminal (intravascular) and abluminal cues, integrating brain and body signals to gate transmission of body-state information. Increases in EC intracellular Ca2+ drives BBB permeability in vitro, we therefore simultaneously imaged BBB permeability and EC Ca2+. We find that Plume Events are tightly linked to EC Ca2+ Events (ECCE). Focal ECCE, previously characterized in ex vivo and anesthetized preparations, are imaged here in awake, behaving animals. We find ECCE are frequent and fast, peaking ~500 ms after the sensory cue with a mean duration of ~1.9 s. Critically, Plume Events are ~2-fold more likely to onset within 0 to 2 s of an ECCE and show a larger footprint when ECCE-predicted. These data support a 'State-Gate' hypothesis: Rather than passively leaking, the BBB transiently permits permeability when the behavioral value of sampling body state outweighs the risk of contamination, with ECCE setting the gate. Together, these findings reposition the endothelium as an active, state-dependent regulator of rapid BBB permeability, linking cellular vascular signaling to brain state and behavior.

Disclosures: K.L. Turner: None. **S. Fekir:** None. **S.J. Scott:** None. **C. Johnson:** None. **C.I. Moore:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.18/HH27

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant F31NS147788 (to J.C.W)
Shuri and Kay Curci Foundation Award (to E.A.W)
Marcus Precision Medicine Grant (to E.A.W)
Cerebrovascular Section / Congress of Neurological Surgeons Foundation Young Investigators Research Grant (to E.A.W)

Title: Spatially resolved molecular cartography reveals specialized cell ensembles in the human brain vasculature

Authors: *J. WANG, E. WINKLER;
Neurolog. Surgery, Univ. of California, San Francisco, San Francisco, CA

Abstract: The human brain vasculature is a highly specialized, segmentally organized network that supports nutrient delivery, blood-brain barrier transport, neurovascular coupling, and immune surveillance, yet its spatial logic in the human brain remains poorly defined. We integrated 5 vascular-enriched human single-cell and single-nucleus RNA-seq datasets from 39 donors to generate a unified cerebrovascular atlas comprising 314,535 transcriptomes, then designed 300-gene Xenium panels to perform cell-resolution spatial transcriptomics across the temporal cortex and hippocampus, mapping 1,529,740 cells. This framework resolved consensus endothelial, mural, fibroblast, and perivascular macrophage states spanning the full arteriovenous axis and identified stereotyped multicellular micro-communities, termed vascular cell ensembles. These ensembles comprised specialized endothelial cells, smooth muscle cells, pericytes, fibroblasts, and perivascular macrophages that aligned with vascular segment identity and organized into leptomeningeal macrovascular and intraparenchymal microvascular niches. Endothelial zonation patterns were conserved across cortex and hippocampus, whereas mural and perivascular populations showed region-specific tuning. Matrix pericytes localized preferentially to arteriolar and venular segments, transport pericytes to capillaries, and fibroblast subsets to meningeal and perivascular niches. Spatial analyses further revealed that cortical and hippocampal microvasculature follow conserved organizing principles despite marked cytoarchitectural differences, while hippocampal vessels showed distinct microvascular composition consistent with regional specialization. Cross-species comparisons showed conservation of endothelial zonation with human-specific mural specialization. Ensemble-level analyses linked arterial and arteriolar ensembles to vasomotor and neurovascular coupling programs, capillary ensembles to blood-brain barrier transport, and venular and venous ensembles to immune surveillance. Integration of genetic risk and predicted pharmacologic reactivity further identified ensemble-selective disease associations and therapeutic vulnerabilities, including mural cell enrichment in small vessel disease and stroke, perivascular macrophage association with Alzheimer’s disease risk, and segment-selective therapeutic targets. These findings define the spatial logic of the human cerebrovasculature and establish vascular cell ensembles as a framework linking vascular cell identity, vessel segment specialization, and neurological disease vulnerability.

Disclosures: J. Wang: None. **E. Winkler:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.19/HH28

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH F31NS145737
NIH T32NS136080
NIH R01DA050159

Title: Dendritic Ca^{2+} activity of layer 5 pyramidal neurons as a near-perfect proxy of resting state hemodynamics

Authors: *B. C. RAUSCHER[1], N. FOMIN-THUNEMANN[1], N. X. CHAI[2], J. X. JIANG[1], D. BOGATOVA[3], M. THUNEMANN[1], A. DEVOR[1];
[1]Biomed. Engin., [2]Undergraduate program in Neurosci., [3]Biol., Boston Univ., Boston, MA

Abstract: Hemodynamic imaging technologies often rely on the concept of the *impulse response function (IRF)* that links neural activity to hemodynamics. Recently, using widefield optical imaging across the dorsal cerebral cortex in mice expressing jRGECO Ca^{2+} sensor in all excitatory neurons, we showed that the Ca^{2+} signal alone was a poor predictor of total hemoglobin (HbT, indicative of vasodilation)[1]. In that study, addition of a second IRF based on norepinephrine (NE) improved the HbT prediction, particularly in the anterior cortical region MOs[1].
Because the depth penetration of widefield imaging is limited to the top ~300 um, we reasoned that the jRGECO Ca^{2+}signal reflected, at least in part, activity of the apical dendrites of cortical pyramidal neurons (PNs). Therefore, in this study, we used both mesoscopic and 2-photon imaging in Rbp4-cre mice expressing the GCaMP7s Ca^{2+} sensor in layer 5 PNs (L5PNs). Remarkably, Ca^{2+} signals provided a near-perfect proxy for HbT everywhere except MOs (**Fig. 1**). Next, we used 2-photon microscopy to measure vasodilation of single penetrating arterioles simultaneously with either dendritic or somatic Ca^{2+} (in L5PNs). Consistent with widefield imaging, we observed high correlation of vasodilation and dendritic Ca^{2+}. However, there was only weak correlation of vasodilation and somatic Ca^{2+}. Experiments are underway to determine whether addition of NE improves HbT prediction in MOs.
Excitability of the apical dendrites of L5PNs is regulated by neurons expressing vasointestinal peptide (VIP) within the “disinhibition circuit” as well as by acetylcholine (ACh); both VIP and ACh are vasodilators. Upon excitation, the apical dendrites might release a vasodilator prostaglandin E_2. Experiments are underway to examine the role of these neurochemicals in driving vasodilation. Unraveling these mechanisms would open the door for inference of neuronal circuit activity with molecular specificity from hemodynamics.

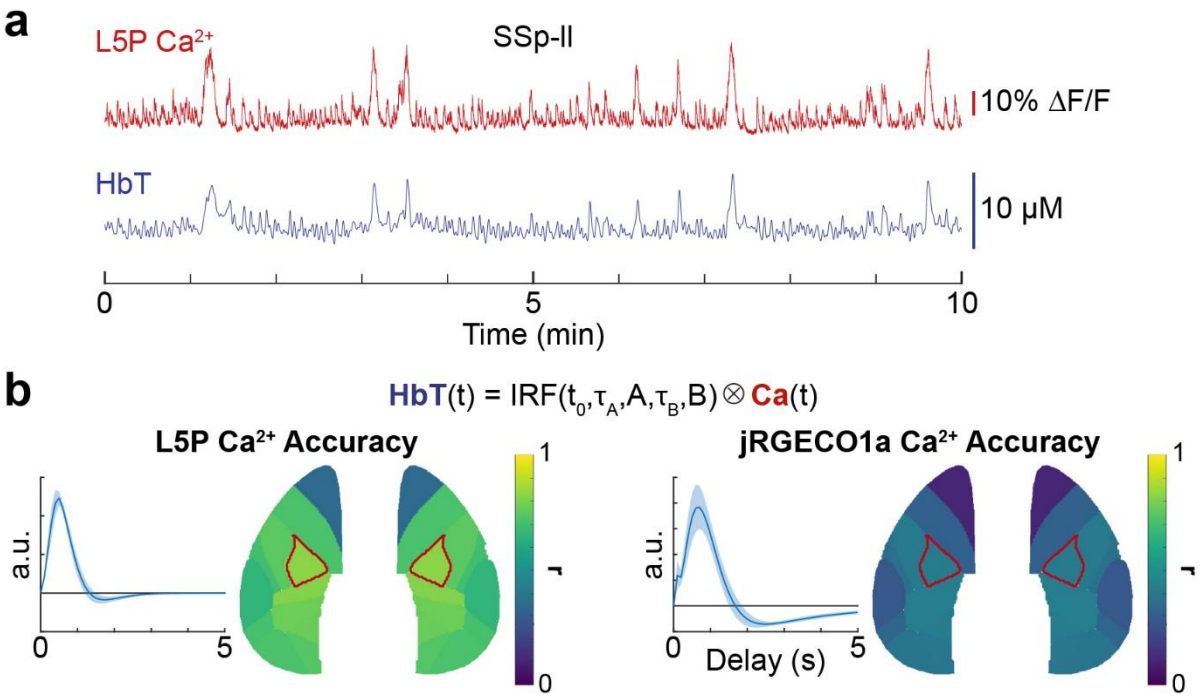


Fig. 1: Dendritic Ca^{2+} activity of L5PNs and HbT. **a)** L5PN Ca^{2+} activity and HbT from SSp-ll cortical region. **b)** Estimated IRF and accuracy of HbT prediction (correlation between predicted and experimental HbT) using L5PN Ca^{2+} (left) and Thy1_jRGECO1a Ca^{2+} (right).

1. Rauscher, B.C., Fomin-Thunemann, N., et al. 2026. Nature Neuroscience. https://doi.org/10.1038/s41593-026-02239-7

Disclosures: B.C. Rauscher: None. **N. Fomin-Thunemann:** None. **N.X. Chai:** None. **J.X. Jiang:** None. **D. Bogatova:** None. **M. Thunemann:** None. **A. Devor:** None.

Poster

PSTR238: Cerebral Hemodynamics and Signaling at the Neurovascular Interface

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR238.20/HH29

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: U19NS123717
R01NS121095
R01NS115401
R01AG081841
U24EB028941

Title: Arousal-dependent modulation of vasomotion and low-frequency intravascular pO_2 dynamics in aging versus young mouse brains

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Abstract: Vasomotion may contribute to the regulation of cerebral microvascular perfusion and oxygen delivery at rest. Meanwhile, both arousal states and aging profoundly influence cerebral hemodynamics by altering vascular tone and cerebrovascular function. However, the role of vasomotion in shaping oxygen dynamics across arousal states and aging remains incompletely understood.
To address this question, we used two-photon microscopy (2PM) to simultaneously measure vascular diameter and intravascular pO_2 fluctuations in surface and penetrating vessels of awake C57BL/6 mice at rest across three age groups: young (5-7 months, n = 8), middle-aged (11-13 months, n = 8), and aged (17-19 months, n = 5). Pupil diameter was continuously monitored as an indicator of arousal state.
We found that mean arteriolar diameter, venular diameter, and venular pO_2 were predominantly modulated by arousal state, decreasing by 4.2-4.8 μm, 1.9-2.4 μm, and 9.7-12.3 mmHg, respectively, when transitioning from low to high arousal across all age groups. In contrast, mean arteriolar pO_2 was primarily reduced by aging rather than arousal state, with young mice showing higher arteriolar pO_2 than aged mice by 9.4 mmHg and 6.3 mmHg under low- and high-arousal conditions, respectively, and only a modest increase with arousal.
Welch power spectral density (PSD) analysis revealed relatively similar amplitude of arteriolar vasomotion around ~0.1 Hz under low-arousal conditions across all age groups (−18.3 to −17.9 dB/Hz). However, the spectral power in this frequency range was substantially attenuated during high arousal, particularly in middle-aged and aged mice (~3-4 dB reduction), indicating that aging selectively impairs arousal-dependent vasomotion. In contrast, the low-frequency PSD of pO_2 increased in both arterioles and venules under elevated arousal states over a broader frequency range (0.1-0.3 Hz), especially in venules, whereas aging exerted comparatively weaker effects. Coherence analysis revealed strong coupling between arteriolar diameter and venular pO_2 fluctuations in the 0.05-0.40 Hz band (coherence ~0.6) across arousal states in young mice, with arteriolar diameter leading venular pO_2, suggesting that blood flow changes are a dominant — though not exclusive — driver of venular pO_2 dynamics in this frequency range. Our findings reveal that arousal state and aging exert distinct and dissociable effects on vasomotion and intravascular pO_2 dynamics, with implications for understanding cerebrovascular dysregulation in aging.

Disclosures: Q. Pian: None. **Y. Zhou:** None. **B. Fu:** None. **M. El Khatib:** None. **J. Tang:** None. **S.A. Vinogradov:** None. **X. Yu:** None. **J.R. Polimeni:** None. **D. Kleinfeld:** None. **A. Devor:** None. **S. Sakadzic:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.01/HH30

Topic: G.07. Biological Rhythms and Sleep

Support: Coordination for the Improvement of Higher Education Personnel (CAPES), Brazil
Research Support Foundation of the Federal District (FAPDF), Brazil

Title: Too Late to Train? Revisiting the Effects of Evening Physical Activity on Sleep

Authors: *R. L. OLEGARIO, RLO[1], E. F. VIEIRA[2], C. GOULART[2], L. L. L. MARTINI[2], E. F. CAMARGOS[2];
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Abstract: Traditional sleep hygiene recommendations often discourage exercise during the evening because of concerns regarding physiological arousal and impaired sleep. However, emerging evidence suggests that evening physical activity may improve sleep quality. We conducted a systematic review and meta-analysis to evaluate the effects of evening exercise on objectively measured sleep outcomes in adults. A systematic search was conducted in Cochrane Library, Embase, PubMed, Scopus, Web of Science, and Google Scholar according to PRISMA guidelines. Following screening and eligibility assessment, 19 studies met inclusion criteria for the systematic review. Of these, 11 studies provided sufficient quantitative data for meta-analysis. Eligible studies investigated acute or chronic evening exercise interventions and reported objective sleep outcomes measured using polysomnography, actigraphy, or validated sleep-monitoring devices. Random-effects meta-analyses were performed using restricted maximum likelihood estimation with Knapp-Hartung adjustment. Mean differences (MD) were calculated for sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency (SE). Evening exercise significantly reduced SOL (MD = −4.33 min, 95% CI: −7.92 to −0.74, $p = 0.023$), indicating faster sleep initiation. WASO was significantly reduced (MD = −12.23 min, 95% CI: −17.58 to −6.88, $p < 0.001$), demonstrating improved sleep maintenance. Sleep efficiency increased significantly following evening exercise (MD = +3.41%, 95% CI: 1.03 to 5.78, $p = 0.010$). Heterogeneity was substantial for SOL ($I^2 = 94.6\%$), low for WASO ($I^2 = 24.9\%$), and moderate for SE ($I^2 = 60.6\%$). These findings challenge traditional recommendations discouraging evening exercise and suggest that physical activity performed during the evening may be associated with improvements in objectively measured sleep outcomes in adults. Further research is needed to determine the mechanisms underlying these associations and their potential implications for brain health across adulthood.

Disclosures: R.L. Olegario: None. **E.F. Vieira:** None. **C. Goulart:** None. **L.L.L. Martini:** None. **E.F. Camargos:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.02/HH31

Topic: G.07. Biological Rhythms and Sleep

Title: Long-term changes in the patterns of sleep and blood pressure data following repeated COVID-19 infection

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Abstract: This long-term study, conducted from December 30, 2020, to May 26, 2026, includes self-reported data from a participant who experienced two mild SARS-CoV-2 infections and received four subsequent mRNA-based vaccinations. The infections occurred in 2021 (Ct = 34.42) and 2022 (Ct = 27.09, Omicron), both on March 10. The entire 5.4-year period was divided into five distinct phases: a pre-covid phase (70 days), a post-covid-1 phase (350 days), a post-covid-2 phase (770 days), a post-covid-3 phase (392 days), and a post-covid-4 phase (364 days). The analysis encompassed activity data and internal medical parameters (daily steps, body temperature, weight/body mass index, blood pressure, heart rate, VO2max, pulse wave velocity), as well as sleep data (REM, DEEP and LIGHT sleep, total/restorative sleep). The subject's baseline examination prior to the pre-covid phase revealed no changes in blood pressure or sleep architecture. In the post-Covid-1 phase, systolic blood pressure levels exhibited an increase ($P=0.0001$). The duration of the light sleep phase decreased ($P=0.0094$). A significant increase in heart rate was observed during both the day and nighttime periods ($P=0.0001$). As a result of the Omicron infection, the post-COVID-2 phase is characterized by an increase in systolic and diastolic blood pressure ($P=0.0001$ for both) and, with regard to sleep parameters, a prolongation of the LIGHT phase ($P=0.0056$) and a significant decrease in the REM and DEEP phases ($P=0.0001$ for each). In the post-Covid-3 phase, a substantial decrease in systolic ($P=0.0036$) and diastolic ($P=0.0010$) blood pressure parameters was observed. While the DEEP phase remains constant, the duration of the REM phase ($P=0.0005$), the LIGHT phase ($P=0.0003$) and the total sleep duration increased ($P=0.0007$). The post-Covid-4 phase is characterized by the absence of substantial alterations in blood pressure readings. The research findings indicated that there was an increase in the values for the REM phase ($P=0.0176$) and the DEEP phase ($P=0.0018$). Conversely, a decrease was observed in the LIGHT phase ($P=0.0165$). The restorative phase exhibited a substantial increase ($P<0.0001$), while total sleep duration remained constant. The results indicate that 50 months following the second instance of SARS-CoV-2 infection, blood pressure levels maintain stability, remaining marginally elevated above pre-infection baselines. DEEP values have surpassed pre-pandemic levels, while REM values remain below them. Only LIGHT values have returned to the baseline range. Restorative sleep duration demonstrated an increase that fell slightly below the baseline level from the pre-pandemic period.

Disclosures: D.M. Weinert: None. **H.D. Bennefeld:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.03/HH32

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R01AG070227
NIH Grant R01AG081693

Title: From Sensorimotor to Transmodal Cortex: Sleep Quality Aligns Brain Entropy with the Cortical Functional Gradient

Authors: *G. DEL MAURO[1], Y. LI[1], J. YU[2], P. KOCHUNOV[3], H. RAO[4], Z. WANG[1]; [1]Dept. of Diagnos. Radiology and Nuclear Med., Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Dept. of Mathematics, Univ. of Maryland Col. Park, College Park, MD; [3]Dept. of Psychiatry and Behavioral Sci., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [4]Ctr. for Magnetic Resonance Imaging Res. & Key Lab. of Brain-Machine Intelligence for I, Shanghai Intl. Studies Univ., Shanghai, China

Abstract: Sleep is essential for maintaining optimal brain function, yet its influence on large-scale neural dynamics during wakefulness remains poorly understood. We investigated whether habitual sleep quality is associated with regional and network-level temporal complexity of spontaneous brain activity. Regional brain entropy (BEN), a measure of the temporal irregularity of spontaneous neural activity, and cross-regional brain entropy (CRBEN), a measure of similarity in temporal complexity between brain regions, were estimated from resting-state fMRI data in 32,889 participants from the UK Biobank. Findings were evaluated in an independent Human Connectome Project (HCP) cohort (N = 1,941) and in an experimental total sleep deprivation study (N = 44). Associations between sleep measures and entropy metrics were assessed at regional and network levels. Spatial correspondence between sleep-related BEN effects and the principal cortical functional gradient was evaluated using spin-test permutation analyses. Better sleep quality was associated with higher BEN in visual, somatomotor, and posterior cortical regions and lower BEN in frontoparietal control regions. At the network level, better sleep quality was associated with increased CRBEN among sensory and sensorimotor systems and reduced CRBEN within higher-order control networks. The regional pattern of sleep-related BEN effects was strongly aligned with the principal cortical functional gradient ($\rho = -0.79$, $p_{spin} < 0.001$). In the independent HCP cohort, greater sleep duration was associated with increased BEN and CRBEN in visual and somatomotor regions and showed a similar gradient-aligned spatial organization ($\rho = -0.82$, $p_{spin} < 0.001$). Similar entropy alterations were observed following experimental sleep deprivation. These results show that habitual sleep quality is associated with systematic reorganization of the brain's temporal complexity architecture during wakefulness. Sleep-related effects follow the cortex's principal functional gradient, suggesting that sleep modulates neural dynamics along a hierarchical axis linking sensory and transmodal systems.

Disclosures: G. Del Mauro: None. **Y. Li:** None. **J. Yu:** None. **P. Kochunov:** None. **H. Rao:** None. **Z. Wang:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.04/II1

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01 DC004290-22

Title: Mapping spindle features in sleep and under anesthesia using higher-order spectra in human intracranial recordings

Authors: *O. COX[1], B. J. DLOUHY[1], A. E. RHONE[1], C. K. KOVACH[2], S. KUMAR[1]; [1]Dept. of Neurosurg., Univ. of Iowa, Iowa City, IA; [2]Dept. of Neurosurg., Univ. of Nebraska, Omaha, NE

Abstract: Sleep spindles are transient bursts of brain oscillations in the 11-16 Hz range that are a hallmark of non-REM sleep. While traditionally linked to sleep, remarkably similar spindle-like activity also occurs under anesthesia. However, the precise differences in their anatomical origins and waveform features remain poorly understood. In this study, we investigated spindle dynamics by analyzing local field potentials (LFPs) from intracranial depth electrode recordings in human subjects (n=7), where data from the same subjects were collected under both sleep and propofol anesthesia. To automatically detect these spindles and map their distinct features, we utilized advanced signal processing methods based on Higher-Order Spectra (HOS)—specifically, a fourth order trispectrum framework developed by our group (Kovach and Kumar, under review). Our analysis revealed the following differences between sleep and anesthesia. First, the origin of spindles varied significantly. During sleep, spindles spanned a widely distributed network of cortical and subcortical structures, including the thalamus, sensory-motor cortex, and frontal and temporal regions. In contrast, under propofol anesthesia, distribution of spindles shifted towards the thalamus with both an increase in likelihood of observing spindles in thalamic sites (OR=1.6, linear mixed-effects model: $p<0.01$) and a decrease in observations in non-thalamic sites (OR=0.5, linear mixed-effects model: $p<0.001$). Second, we observed a distinct divergence in intra-spindle frequency dynamics during individual spindle time windows: Spindle frequency increased over time under anesthesia (positive chirp), whereas it decreased over time during sleep (negative chirp). Third, the time-duration of spindles was significantly greater ($p<0.001$) under anesthesia compared to sleep. Fourth, the majority of thalamic spindles occurred in the posterior ventrolateral nucleus under anesthesia compared to the pulvinar during sleep. Our findings suggest a model of disrupted thalamo-cortical communication during propofol anesthesia. Kovach, C., Kumar, S: Modulation Analysis with Higher-Order Spectra, PLOS Computational Biology (under review)

Disclosures: O. Cox: None. **B.J. Dlouhy:** None. **A.E. Rhone:** None. **C.K. Kovach:** None. **S. Kumar:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.05/II2

Topic: G.07. Biological Rhythms and Sleep

Support: 5UH3NS113769

Title: Spindle Morphology as a Biomarker of Thalamocortical Integrity

Authors: *C. K. KOVACH[1,4], S. KUMAR[4], O. COX[4], S. V. GLISKE[2], S. MATHEW[3], A. ABOSCH[5];
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Abstract: Introduction: Sleep spindles—11-16 Hz oscillatory bursts —emerge from thalamocortical interactions during non-REM sleep and anesthesia. Alteration of spindle morphology may serve as a sensitive biomarker of disordered thalamocortical connectivity. Existing methods for measuring spindle morphology lack precision and reliability.**Methods:** We applied a new technique for measuring spindle morphology, based on estimation and decomposition of the fourth-order spectrum (trispectrum). This approach recovers aggregate spindle properties —carrier frequency, duration, and intra-spindle slope— from time-averaged statistics without the need to identify spindles as a prior step, avoiding biases and limitations introduced by spindle detection. The method was validated in 100 whole-night polysomnograms from the MASS open database and applied to compare spindle morphology during sleep and propofol anesthesia in intracranial recordings from 9 epilepsy patients.**Results:** Across 100 polysomnograms, we observed a highly specific and robust signature of spindle-band modulation in the trispectrum. Trispectral phase revealed negative intra-spindle frequency slope in all but one recording (median −3.9 Hz/s, $P \ll 0.001$). Negative spindle slope was similarly observed in intracranial recordings from 9 epilepsy patients during sleep. Spindles distributed broadly across cortical and subcortical sites. Those occurring under anesthesia in the same patients exhibited no consistent slope, and their anatomical distribution shifted toward the thalamus.**Conclusion:** We demonstrate a novel method for characterizing spindle morphology based on the trispectrum. Loss of intra-spindle deceleration and the shift toward thalamic generators under anesthesia are consistent with disrupted thalamocortical connectivity, highlighting spindle morphology as a biomarker of thalamocortical function.

Disclosures: C.K. Kovach: None. **S. Kumar:** None. **O. Cox:** None. **S.V. Gliske:** None. **S. Mathew:** None. **A. Abosch:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.06/II3

Topic: G.07. Biological Rhythms and Sleep

Support: NSF
HHMI

Title: Dream Walking: The Representation of Locomotion in the Brain During REM Sleep

Authors: *S. GRUTZNER[1], M. SCANZIANI[2];
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Abstract: In dreams we wander, while remaining stationary in bed. Is the brain simulating locomotion during sleep in the same way it enacts it during wakefulness? In pursuit of this question, we focused on the mesencephalic locomotor region (MLR), a functionally defined brainstem area that controls locomotion. Recording from the MLR in freely moving mice confirmed the presence of neurons whose activity accurately predicted locomotion as the animals explored an open field. Animals then fell asleep and standard electrophysiological metrics were used to classify Rapid-Eye Movement (REM) and Non-REM (NREM) sleep states. We observed a striking sleep-state dependent activity change in locomotion-modulated neurons in MLR. During NREM sleep these neurons became virtually silent, whereas during REM sleep their activity returned to awake levels. Interestingly, during REM sleep, locomotion-modulated neurons were active in bouts whose durations resembled those observed during wakefulness. Furthermore, neurons that were active together during wakefulness were also active together during REM sleep, while neurons whose activity was inversely related during wakefulness maintained that same relationship during REM sleep. The coordinated activity of MLR locomotion-modulated neurons during REM sleep mimicked their dynamics during natural walking to such a degree that a decoder trained during wakefulness mistakenly predicted the immobile sleeping animal to be walking. That this activity emerges during REM sleep, a state defined by vivid dreaming and complete immobility, suggests that an internal representation of locomotion exists within the MLR.

Disclosures: S. Grutzner: None. **M. Scanziani:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.07/II4

Topic: G.07. Biological Rhythms and Sleep

Support: National Natural Science Foundation of China (82130040)

Title: Chronic stress biases brain-state transitions toward REM sleep through reorganization of dorsal raphe-prefrontal circuit dynamics

Authors: *X. LI[1], T. LU[1], S. MENG[1], J. SHI[2];
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Abstract: Sleep disturbances are a major consequence of chronic stress and are strongly associated with affective disorders. Increased rapid eye movement (REM) sleep is frequently observed following prolonged stress exposure. However, the circuit mechanisms underlying this phenomenon remain poorly understood. Here, we investigated how chronic restraint stress (CRS) remodels dorsal raphe nucleus (DRN)-medial prefrontal cortex (mPFC) circuit function to regulate REM sleep. Adult mice were subjected to CRS (3 h/day for 10 consecutive days) and monitored using chronic EEG/EMG recordings. CRS selectively increased REM episode number, and reduced latency to REM onset, indicating a stress-induced bias toward REM-state transitions. Fiber photometry recordings revealed that CRS profoundly altered neural dynamics in both the DRN and mPFC preceding REM onset. Specifically, stress enhanced prefrontal activity and disrupted normal DRN-mPFC coordination during transitions into REM sleep, suggesting that chronic stress reorganizes brainstem-cortical activity patterns before REM generation.To determine the causal role of this pathway, we performed projection-specific manipulations of DRN neurons projecting to the mPFC. Inhibition of the DRN→mPFC pathway attenuated stress-induced REM enhancement, whereas activation of the same pathway increased REM sleep in unstressed animals and facilitated transitions into REM. Ex vivo electrophysiological recordings further demonstrated stress-dependent remodeling of DRN inputs onto prefrontal excitatory neurons. Consistent with these findings, selective manipulation of mPFC excitatory neuronal activity bidirectionally regulated REM sleep and occluded the effects of DRN→mPFC circuit modulation. Finally, neural population activity within the DRN-mPFC circuit reliably predicted upcoming REM transitions, enabling successful closed-loop modulation of REM sleep in real time. Together, these findings identify a brainstem-prefrontal circuit mechanism through which chronic stress biases brain-state transitions toward REM sleep and establish DRN-mPFC dynamics as a key substrate for stress-induced sleep dysregulation.

Disclosures: X. Li: None. **T. Lu:** None. **S. Meng:** None. **J. Shi:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.08/II5

Topic: G.07. Biological Rhythms and Sleep

Title: Effects of APOE genotype on resting-state functional connectivity across wakefulness and sleep

Authors: ***C. GOMES**[1], L. DEUKER[1], H. LEE[2], N. AXMACHER[1];
[1]Ruhr Univ. Bochum, Bochum, Germany; [2]German Ctr. For Neurodegenerative Dis. (DZNE) Bonn, Bonn, Germany

Abstract: Sleep disruptions and accompanying changes in brain connectivity are increasingly recognised as features of Alzheimer's disease (AD). However, it remains unclear how genetic risk and protective factors for AD, particularly APOE genotype, influence functional connectivity during specific sleep stages and whether such differences affect subsequent recognition memory. In this study, we investigated the effects of APOE genotype on resting-state functional connectivity across wakefulness and sleep, focusing on differences between ε2 and ε4 carriers relative to ε3/ε3 individuals, as well as between ε2 and ε4 carriers. Seventy-eight participants were genotyped for APOE. Participants initially completed an encoding task in which they evaluated whether they liked/disliked images of faces or buildings. They then underwent one hour of simultaneous EEG-fMRI recording while sleeping in the scanner. Following sleep, a functional localiser scan was used to identify category-selective brain regions. Finally, a surprise recognition memory test was administered outside the scanner, in which participants decided on a 1 (sure old) to 5 (sure new) scale whether images of faces/buildings had been shown at encoding. Although recognition memory performance did not differ across genotypes, our fMRI analyses revealed greater connectivity between the entorhinal and hippocampal cortices during wakefulness in ε2 carriers relative to both ε3 and ε4 groups. During sleep, ε2 carriers also showed stronger connectivity between entorhinal cortex and the precuneus. Network analysis further indicated that connectivity within the limbic network decreased as a function of performance in ε4 carriers, whereas ε4 carriers exhibited greater connectivity than ε2 and ε3 individuals within specific clusters of the control, somatosensory, and cerebellar networks. Together, these findings suggest that ε2 carriers exhibit enhanced connectivity within limbic networks that may underlie their reduced AD risk. In contrast, wake- and sleep-related limbic circuits may already be vulnerable in ε4 carriers, while enhanced connectivity in non-limbic networks may represent compensatory recruitment of systems that are generally affected later than limbic regions in AD.

Disclosures: C. Gomes: None. **L. Deuker:** None. **H. Lee:** None. **N. Axmacher:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.09/II6

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant DK142148

Title: Antagonistic hypothalamic feeding populations exhibit similar activity dynamics across sleep/wake states independently of sleep pressure

Authors: *C. POLLOCK, E. MOFFETT, M. CARTER;
Williams Col., Williamstown, MA

Abstract: An animal's survival depends on balancing competing homeostatic demands. Among these, feeding and sleeping represent mutually exclusive behaviors. In the hypothalamic arcuate nucleus, agouti-related peptide (AgRP)-expressing neurons and proopiomelanocortin (POMC)-expressing neurons promote hunger and satiety signaling, respectively, to regulate feeding. Previous studies show that both artificial activation and fasting-induced increases in AgRP neuron activity promote wakefulness, whereas inhibition of AgRP neurons or activation of POMC neurons restores normal sleep patterns in food-deprived mice. However, how these neuronal populations are naturally regulated across sleep/wake states remains unclear. Here, we combined fiber photometry with electroencephalography (EEG) and electromyography (EMG) recordings to monitor AgRP and POMC neuron activity across naturally occurring sleep/wake transitions in male and female mice. As expected, food presentation elicited opposing responses in these populations, suppressing AgRP activity while increasing POMC activity, confirming their canonical feeding-related functions. We hypothesized that sleep onset would require suppression of AgRP neurons with reactivation upon waking, whereas POMC neurons would exhibit inverse activity changes. Contrary to this hypothesis, AgRP and POMC neurons displayed strikingly similar activity dynamics across most vigilance-state transitions. Both populations showed minimal changes during Wake-to-NREM transitions, increased activity during NREM-to-REM transitions, and decreased activity upon REM-to-Wake transitions. The principal exception was the transition from NREM sleep to wakefulness, during which AgRP activity decreased while POMC activity increased. Similarly, brief microawakenings were associated with transient suppression of AgRP activity but little change in POMC activity. Importantly, these state-dependent activity patterns persisted following sleep deprivation, indicating that they are largely independent of elevated sleep pressure. Together, these findings reveal that antagonistic hypothalamic feeding populations are regulated in a surprisingly coordinated manner across sleep and wake states. Rather than reflecting hunger and satiety signaling alone, AgRP and POMC activity appears strongly constrained by global brain-state architecture, allowing feeding-related circuits to remain integrated within ongoing sleep processes without overriding behavioral state.

Disclosures: C. Pollock: None. **E. Moffett:** None. **M. Carter:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.10/II7

Topic: G.07. Biological Rhythms and Sleep

Support: 2014217/NSF | Next Generation Network for Neuroscience (NeuroNex)
CC2036/Crick/Wellcome Trust/CRUK/UKMRC/Grant Ref MC_UP_1202/5
Wellcome Trust Investigator Grant 110174/Z/15/Z (to A.T.S.)

Title: State-dependent geometry of representational drift across wake and sleep

Authors: *J. J. HARRIS[1], A. T. SCHAEFER[2], M. KOLLO[3];
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Abstract: Neural representations evolve over time, yet the relative contributions of online experience and offline states such as sleep remain unclear. Here, we recorded single-unit activity in the olfactory cortex of mice across cycles of awake odour exposure and sleep, and developed a low-rank decoder to track representational drift. We identified four orthogonal drift modes operating on distinct timescales, revealing that sleep and wake drive qualitatively different transformations, which indicates that offline reorganisation is not a simple continuation of online learning. Rather, sleep initiates an about-turn in the overall drift trajectory, which is uniquely characterised by a combination of decorrelation and rotation of odour representations. We also provide the first evidence for olfactory replay, occurring at ~2.5x temporal compression and associated with locally generated piriform cortex sharp waves. Together, these findings demonstrate that representational drift comprises state-dependent components, and reveal distinct contributions of wake and sleep to sensory representational change.

Disclosures: J.J. Harris: None. **A.T. Schaefer:** None. **M. Kollo:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.11/II8

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant U19NS128613
US Army Research Office MURI W911NF1910280
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
Simons Foundation Grant 811237

Title: Perivascular fluid flow along brain capillaries is a novel component of the glymphatic system

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Abstract: Despite its exceedingly high metabolic activity, the brain lacks a traditional lymphatic system. Instead, waste is cleared via cerebrospinal fluid (CSF) circulation through the glymphatic system, a network of perivascular spaces (PVSs) surrounding arteries and veins. CSF flow within arterial PVSs is well characterized while the features, and even existence, of capillary PVSs remain understudied. To determine the existence of capillary PVSs we developed a novel in vivo imaging approach combining high concentration tracer infusion with 2-photon imaging using parameters sensitive to lower signal intensities. These experiments were performed in male and female wild-type C57BL6 mice aged 8-12weeks old. A timecourse of tracer influx into the brain tissue post infusion demonstrated that the CSF tracer concentration within brain tissue reached a plateau after roughly 60 minutes (n=6 mice). Further, we found brighter tracer signal along capillaries than adjacent brain parenchyma, consistent with a larger fluid compartment along capillaries(n=7 mice, 127 capillaries). We confirmed that the tracer accumulated along capillaries exists within a mobile compartment by using fluorescent recovery after photobleaching (FRAP) (n=7 mice, 72 capillaries). CSF movement through the glymphatic system is well known to be upregulated during sleep. We found slower movement of tracer in awake(n=7 mice, 86 capillaries) compared to anesthetized animals (n=7 mice, 72 capillaries). The existence and brain state regulation of capillary PVSs is informative for modeling the organization of the glymphatic system and adds to the understanding brain metabolic waste clearance. This new approach can be used to further investigate capillary PVSs in settings known to impact glymphatic flow and remodel blood vessels such as traumatic brain injury, stroke, or normal aging.

Disclosures: M.J. Giannetto: None. **M. Nedergaard:** A. Employment/Salary (full or part-time):; CNS2.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.12/II9

Topic: G.07. Biological Rhythms and Sleep

Support: NIH, R01NS110012
Army Research Office, W911NF-24-1-0013
Howard Hughes Medical Institute

Title: Parabrachial Tac1 neurons drive large ~12h circadian phase shifts through a nonphotic fear pathway

Authors: *V. Y. ZHANG[1], S. PARK[3], J. PAULI[2], K. DERDERIAN[4], R. D. PALMITER[4], H. O. DE LA IGLESIA[5];
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Abstract: Circadian rhythms in mammals are classically entrained by light, but nonphotic cues can also reorganize behavior through mechanisms that remain poorly understood. In nocturnal rodents, a cyclic aversive stimulus can act as a potent nonphotic cue: footshocks delivered at night, while animals forage outside the safety of their nest, shift circadian behavioral rhythms into the daytime ("fear entrainment"). Here, we identify components of the circuitry underlying fear entrainment. The parabrachial nucleus (PBN) is a brainstem alarm hub, and optogenetic activation of tachykinin 1 (Tac1)-expressing PBN ($Tac1^{PBN}$) neurons is sufficient to elicit rapid defensive responses. To probe their role in fear entrainment, we used an optogenetic caging system that delivered location- and time-specific stimulation over 10-14 days, with parameters analogous to those used in prior footshock studies. Time-specific local activation of $Tac1^{PBN}$ neurons, but not calcitonin gene related peptide (CGRP)-expressing PBN neurons, recapitulated the ~12 h phase delay elicited by nocturnal footshocks. Blocking synaptic output from $Tac1^{PBN}$ neurons with tetanus toxin (TeTx) abolished fear entrainment, confirming that $Tac1^{PBN}$ synaptic transmission is necessary for the effect. Because an intact amygdala is required for fear entrainment and PBN neurons collateralize strongly to targets in the extended amygdala, including the central amygdala (CeA) and bed nucleus of the stria terminalis (BNST), we tested whether this PBN-amygdala circuitry is engaged during fear entrainment. Stimulating $Tac1^{PBN\rightarrow CeA}$ and $Tac1^{PBN\rightarrow BNST}$ projections produced significant but smaller phase shifts than direct stimulation of $Tac1^{PBN}$ cell bodies, suggesting that multiple downstream targets and/or recruitment of local PBN circuitry contribute to the full effect. Together, these data delineate a parabrachial-amygdala circuit that encodes cyclic aversive stimuli to reorganize circadian foraging and feeding behavior, and they highlight the CeA and BNST as prominent nodes within the circadian fear-entrainable oscillator network. To our knowledge, this is the first demonstration that targeted activation of a defined non-SCN neuronal population is sufficient to drive stable ~12 h circadian phase shifts that emulate nonphotic entrainment.

Disclosures: V.Y. Zhang: None. **S. Park:** None. **J. Pauli:** None. **K. Derderian:** None. **R.D. Palmiter:** None. **H.O. de la Iglesia:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.13/II10

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant EY034617

Title: Cortical inhibitory circuit mechanisms of sleep fragmentation in a mouse model of Down syndrome

Authors: *N. PEREZ CATALAN[1], G. TERRAL[3], R. BATISTA-BRITO[2];
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NY; [3]Dominick P. Purpura Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New-York City, NY

Abstract: Sleep disturbances are highly prevalent in Down syndrome (DS) and may contribute to cognitive dysfunction, yet the cortical circuit mechanisms underlying altered sleep architecture remain poorly understood. Slow-wave sleep is characterized by coordinated low-frequency cortical activity, and recent work from our group identified a group of sparse inhibitory neurons that are selectively active during low-arousal states and sufficient to promote cortical synchrony and sleep. Here, we ask whether DS alters prefrontal slow-wave sleep architecture and whether disrupted recruitment of these inhibitory neurons may contribute to sleep instability. Using 24-hour local field potential recordings from medial prefrontal cortex in Dp16/+ mice and euploid littermate controls, we find preliminary evidence that DS is associated with fragmented NREM sleep, including disrupted delta-rich periods during the light phase, increased transitions out of NREM, and shorter NREM bouts despite preserved or elevated total NREM time. These findings suggest that DS may not simply reduce sleep amount, but instead impair the stability and continuity of slow-wave sleep. To test the circuit basis of this phenotype, we will combine sleep-state scoring and genetic targetting of these prefrontal inhibitory neurons to determine whether their activity is altered during NREM and whether their coupling to delta power and NREM bout stability is disrupted in Dp16/+ mice. Together, this work investigates a cell-type-specific cortical mechanism for sleep disruption in DS and may identify a population of inhibitory neurons as a candidate circuit target for restoring slow-wave sleep dynamics in Down Syndrome.

Disclosures: N. Perez Catalan: None. **G. Terral:** None. **R. Batista-Brito:** None.

Poster

PSTR239: Sleep-Wake Systems

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR239.14/II11

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant K23NS125123 (J.M.F)
Brain and Behavior Research Foundation NARSAD Grant (J.M.F.)

Title: Sleep Subnetworks and Modulatory

Authors: *J. KROLIK[1], J. FAN[1], L. SUGRUE[1], A. LEE[1], A. KRYSTAL[1], D. ASTUDILLO MAYA[2], K. K. SELLERS[3], P. NANDINI[4], L. WANG[5], R. ZHAO[4], A. KHAMBHATI[1]; [2]Psychiatry and Behavioral Sci., [1]Univ. of California, San Francisco, San Francisco, CA; [3]Neurolog. Surgery, UCSF, San Francisco, CA; [4]Univ. of California San Francisco and Univ. of California Berkeley, San Francisco, CA; [5]Univ. of California, San Francisco and Univ. of California, Berkeley, Berkeley, CA

Abstract: Although historically considered a top-down global phenomenon, sleep is increasingly understood to have properties that are locally distributed across the brain. Local sleep has been

associated with homeostatic processes such as localized slowing or spindle activity, but less is known about how subnetworks organize across sleep states. To date, understanding how brain networks reorganize during sleep using intracranial EEG (iEEG) has been limited by electrode placement within epileptogenic tissue. Here, we leverage iEEG in individuals with treatment-resistant depression, without epilepsy, and with consistent coverage spanning the corticolimbic circuit. We recorded 7 patients with multi-night iEEG spanning orbitofrontal cortex, subgenual cingulate, hippocampus, amygdala, thalamus, and ventral capsule/ventral striatum. Phase-locking value (PLV) was computed between all contact pairs within seven frequency bands (delta through high gamma) for each 30-second sleep-staged epoch. Contacts were assigned to parcellated brain regions based on an anatomical atlas, and pairwise PLV was averaged within each region pair. Adjacency matrices were z-scored across epochs, weighted for equal sampling across sleep states. Louvain community detection was applied to identify subnetworks and compute network modularity. Our findings reveal that modularity was sleep-stage and frequency-dependent. Across all frequency bands, modularity differed across sleep stages (linear mixed-effects model; $F(4,46374)>576$, $p<0.001$). In delta and theta, N3 had the lowest modularity (delta Q=0.186; theta Q=0.182), significantly below all other stages (all $p_{adj}<0.001$, Bonferroni-corrected), consistent with global slow-wave synchronization, while wake had the highest (delta Q=0.274; theta Q=0.328). In alpha, REM had the highest modularity (Q=0.304), indicating a frequency-dependent shift. In sigma and beta, this ordering reversed: wake exhibited the lowest modularity (sigma Q=0.188; beta Q=0.128) while REM (sigma Q=0.319) and N3 (beta Q=0.297) showed the highest. Community detection on group-averaged delta connectivity revealed a REM-specific subnetwork comprising bilateral hippocampi and right thalamus (within-community $z=1.50$, permutation $p=0.008$), and a second REM community linking bilateral amygdala, hypothalamus, subgenual cingulate, and orbitofrontal cortex (12 regions, $z=1.16$, $p<0.001$). These findings demonstrate that sleep reorganizes corticolimbic connectivity into frequency-specific local subnetworks.

Disclosures: J. Krolik: None. **J. Fan:** None. **L. Sugrue:** None. **A. Lee:** None. **A. Krystal:** None. **D. Astudillo Maya:** None. **K.K. Sellers:** None. **P. Nandini:** None. **L. Wang:** None. **R. Zhao:** None. **A. Khambhati:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.01/II12

Topic: H.03. Motivation

Support: JSPS KAKENHI 25K02415
JST PRESTO JPMJPR22S4
JST FOREST JPMJFR241R

Title: Striatal dopamine signaling modulates opposing valence-induced learnings

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Abstract: Approaching reward while avoiding aversive events are crucial for survival. Dopamine (DA) in the tail of the striatum (TS) has been discovered as a potential role to signal aversion and induce avoidance learning, though it still remains unknown whether and how the TS DA regulates appetitive learning. To tackle the question, we developed a behavioral task which assessed both reward and aversive learning and monitored TS DA signal using GRAB DA sensor during mice performing the task. The task was a pavlovian conditioning in which the thirsty mouse was exposed to 3 different neutral odors; odor A was followed by water supply, odor B was followed by air-puff stimulation to an eye, and no consequence followed odor C, with 2 seconds interval. The task was performed for 5 consecutive days. Licking and blinking were recorded as the indications for the reward and aversive learning. Anticipatory blinking against odor B, but not A or C, during the delay time was significantly increased across day 1-2 while it was significantly decreased across day 3-5, indicating that the animals learned to avoid the air-puff in early phase while they learned to adapt to it in the later phase. Notably, in the later phase when the air-puff was habituated, anticipatory licking against odor A was significantly increased and it was enhanced in a session where the anticipatory blinking was attenuated. To examine the interference of aversive and appetitive learning directly, we employed weak air-puff group and compared to regular air-puff group. Weak air-puff group showed decreased aversive learning and relatively accelerated appetitive learning. TS DA was specifically activated by air-puff stimulation and its predicting cue. To reveal the roles of TS DA elevation, we removed TS DA. Ablation impaired avoidance learning and accelerated acquiring appetitive learning. In addition, we found that the response of TS DA to aversive conditioned stimulus was decreased in the adaptation phase, when the rate of anticipatory blinking decreased. To understand the behavioral causality, we optogenetically increased TS DA release against air-puff stimulation. Counteracting a decay of TS DA release during the adaptation phase impaired adaptation learning and weakened appetitive learning. In the current study, we demonstrated that 1) our behavioral task is able to address the interference of competing valence-induced learnings, 2) TS dopamine dynamics are essential for avoidance and adaptation to aversive stimuli, which indirectly modulates appetitive learning, underscoring a regulatory mechanism for shifting between defensive and reward-seeking behaviors.

Disclosures: R. Tsuruga: None. **M. Minami:** None. **I. Tsutsui-Kimura:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.02/II13

Topic: H.03. Motivation

Support: F99NS141253
R01MH121009

Title: Interoceptive manipulation enhances avoidance behavior by biasing single-trial ramping activity in the cingulate cortex

Authors: *M. CARDENAS, M. A. KRAUSE, A. PAL, G. NEAL, R. LE, V. MACHAVARAPU, A. A. CORYICROFT, K. M. GOTHARD;
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Abstract: It has long been debated whether bodily signals continuously shape the neural processes that guide behavior or merely follow decisions. Previously, we reported that interoceptive manipulations reduce tolerance to mildly aversive stimuli in rhesus macaques performing a thermal approach-avoidance conflict task. In this task, monkeys tolerated multiple heat levels to receive juice reward or pressed a lever to terminate both heat and reward. Animals received subcutaneously either saline control or glycopyrrolate, a muscarinic antagonist with limited blood-brain barrier penetration that shifts the body into a state of relative sympathetic dominance. Glycopyrrolate increased heart rate and reduced heat tolerance, suggesting that bodily state biases avoidance behavior. While the monkeys performed this task, we recorded single-unit activity from the anterior cingulate cortex (ACC) and amygdala. We observed that 39% of ACC and 18% of amygdala neurons showed ramp-like activity during high heat tolerance. Ramp cells were identified from monotonic changes in firing while the heat remained on. We then asked whether these responses had ramp-to-threshold-like single-trial structure. Individual trials showed consistent monotonic trends in each neuron's ramp direction, rather than step-like changes in firing rate. In addition, spike-count variability decreased near heat termination more strongly in ramp cells than in non-ramp cells, suggesting the presence of a threshold. Ramp-like firing was less prevalent during low-heat trials, when animals rarely terminated the heat. These results indicate that a subset of neurons, especially in ACC, expressed ramp-to-threshold-like activity during high-heat conflict. We next asked which feature of these ramp-like responses best tracked trial-to-trial variability in behavior. In ACC ramp cells, heat tolerance was correlated with within-trial ramp slope; trials where the monkey stopped the heat earlier had steeper slopes. The shorter heat tolerance after glycopyrrolate mapped onto the same slope-behavior relationship observed before administration, suggesting glycopyrrolate influenced heat tolerance through existing task-related mechanisms. These findings suggest that manipulation of afferent interoceptive signals changes avoidance behavior by enhancing the slope of existing ramp-like neural process in anterior cingulate cortex.

Disclosures: M. Cardenas: None. **M.A. Krause:** None. **A. Pal:** None. **G. Neal:** None. **R. Le:** None. **V. Machavarapu:** None. **A.A. Coryicroft:** None. **K.M. Gothard:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.03/II14

Topic: H.03. Motivation

Support: Nu Rho Psi Undergraduate Research Grant

Title: The role of central amygdala CRF projections in incentive motivation

Authors: *K. SHIFFER[1], V. KNAPP[4], A. RAMASWAMI[5], M. POCHOCKI[2], K. EMERY[3], K. C. BERRIDGE[6];
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Abstract: Corticotropin-releasing factor (CRF) neurons are traditionally understood to generate aversive stress states, particularly during withdrawal (Koob & Volkow, 2016). However, emerging evidence suggests that CRF neurons within key limbic structures such as the central amygdala (CeA) may also promote positively valenced motivational states (Baumgartner et al., 2022; Kong & Zweifel, 2021). Specifically, optogenetic stimulation of CRF neurons in the CeA and NAc of *Crh*-Cre rats enhances pursuit of laser-paired sucrose or cocaine rewards over identical rewards without stimulation, while also supporting laser self-stimulation (Baumgartner et al., 2022). These findings suggest that CeA CRF neuron activation contributes to incentive motivation in addition to stress signaling. However, the circuitry underlying this role remains unclear, as the CeA projects locally and to several distant brain regions that may mediate incentive versus aversive valence. To test downstream projection targets, CeA CRF projections to the lateral hypothalamus (LH), ventral tegmental area (VTA), and substantia nigra (SN) were targeted with optogenetics in *Crh*-cre rats. Here, we demonstrate distinct behavioral effects across these projections. In a two-choice sucrose task, where rats can choose between a sucrose pellet paired with laser activation or an identical sucrose pellet without laser, CeA_{CRF}→LH activation biased reward choice for the sucrose without laser and CeA_{CRF}→SN stimulation produced no clear preference, whereas CeA_{CRF}→VTA stimulation produced a significant preference for laser-paired sucrose. However, activating these CRF projections failed to cause a change in magnitude of motivation for sucrose in a progressive ratio breakpoint task. Lastly, it does not appear that rats will consistently self-stimulate any of these projections in either a rod-based or place-based self-stimulation task. Ultimately, we seek to understand how activation of each of these projections impacts c-fos recruitment of brain circuitry involved in both reward and distress.

Disclosures: K. Shiffer: None. **V. Knapp:** None. **A. Ramaswami:** None. **M. Pochocki:** None. **K. Emery:** None. **K.C. Berridge:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.04/II15

Topic: H.03. Motivation

Support: NIH R01MH110425

Title: Neural correlates of safety signaling and fear regulation in the ventromedial prefrontal cortex

Authors: M. PRIVRATSKY[1,2], D. P. LYVERS[1,2], *S. SANGHA[1,2];
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Abstract: The ability to accurately discern between safe and threatening situations is often compromised in stress disorders, leading to maladaptive fear regulation. Individuals with stress disorders show difficulties in conditioned inhibition of fear, which is the downregulation of fear when learned fear and safety cues are presented together (fear+safety cue) compared to when the fear cue is presented alone. Affected individuals also show weaker fear extinction, the reduction of fear when a learned fear cue no longer predicts a threat, compared to controls. Our lab uses well-validated cue discrimination, conditioned inhibition of fear, and fear extinction tasks in male and female Long-Evans rats. In our studies, we observe substantial individual variability in the capacity to regulate fear during conditioned inhibition and fear extinction, which we correlate to differences in neural activity. During this behavior we collected longitudinal single cell calcium activity within the prelimbic (PL) and infralimbic (IL) regions of the ventromedial prefrontal cortex (vmPFC) in freely behaving male and female Long Evans rats using miniscopes and GCaMP expressed via AAV1.GCaMP6m.WPRE.SV40 from Inscopix. We have previously shown that the PL is necessary for fear expression, while the IL is necessary for conditioned inhibition of fear and fear extinction recall. Our current data indicate that there are neurons in the IL that respond selectively to the safety cue during conditioned inhibition, a pattern not observed in the PL. In contrast, PL recordings indicate that following extinction training, a subset of neurons shows reduced responsiveness to the fear cue. Together, these findings identify dissociable and experience-dependent neural coding mechanisms within vmPFC subregions that support distinct aspects of fear regulation. This work provides critical mechanistic insight into how safety signaling and fear attenuation are encoded at the cellular level, offering a translational framework for understanding circuit dysfunction underlying impaired fear regulation in stress-related psychopathology.

Disclosures: M. Privratsky: None. **D.P. Lyvers:** None. **S. Sangha:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.05/II16

Topic: H.03. Motivation

Support: NIH R01MH110425

Title: Second-order conditioning of safety and its orbitofrontal cortex correlates

Authors: *I. F. CALIMAN[1,2], K. CRILOW[1,2], D. GABRIEL[1,2], S. SANGHA[1,2];
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Abstract: In second-order conditioning (SOC) stimuli can gain the ability to elicit learned responses despite never being directly paired with reinforcement. This is in contrast to first-order conditioning where a conditioned stimulus (CS) is directly paired with an unconditioned stimulus (US). Subsequently, if the first-order CS is then paired with a novel stimulus, the learned response can transfer to this novel stimulus even if the US is absent; i.e. SOC. The majority of previous studies have examined SOC of excitatory memories, such as fear or reward, while few studies have investigated the SOC of inhibitory memories, such as safety. Here we show that male and female Long Evans rats, after being trained in our well-stablished first-order safety paradigm, learned SOC of safety. More specifically, animals were first trained in a cue discrimination/feature negative task with 4 types of cue conditions: 1) a reward cue paired with sucrose, 2) a fear cue paired with footshock, 3) a safety cue with no outcome, and 4) the fear and safety cues presented in compound (fear+safety) with no outcome. During the second-order conditioning phase, reward cue+sucrose trials were included alongside trials where a novel stimulus (SOC) was presented followed by the previously learned safety cue. SOC was tested in a probe session including trials of compound fear+safety cues and fear+SOC cues. Our findings demonstrate that a second-order safety cue can attenuate fear responses to a degree comparable to that of a first-order safety cue in both sexes. This demonstrates that female and male rats can transfer safety information to novel stimuli via SOC. We also investigated the role of the orbitofrontal cortex (OFC) in this learning, since its neuronal activity increases during SOC pairings in appetitive contexts, it is correlated with inferred outcome expectations, and it supports outcome encoding in Pavlovian conditioning. Single unit electrophysiological activity in the OFC was collected in freely behaving male and female rats as they proceeded through cue discrimination learning, SOC of safety, and test for SOC. Overall, we have preliminary indications of cue-related modulation in OFC neuronal activity during second-order conditioning of safety. Ongoing analyses are being performed to determine how these signals relate to inferred outcome expectations and how cortical circuits support the flexible encoding of safety.

Disclosures: I.F. Caliman: None. **K. Crilow:** None. **D. Gabriel:** None. **S. Sangha:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.06/II17

Topic: H.03. Motivation

Title: Are measures for anxiety-like behaviors in female Sprague Dawley rats consistent across trials?

Authors: *D. M. RODRIGUEZ, P. GONZALES, S. OSMAN, K. EMERY, A. G. GIBSON;
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Abstract: Are measures for anxiety-like behaviors in female Sprague Dawley rats consistent across trials?AuthorsD. M. Rodriguez, K. Emery, A. G. Gibson; Dept of Psychology and Neuroscience, Regis University,Denver, CO**DisclosuresD. M. Rodriguez**: None, **K. Emery**: None**. A. G. Gibson**: None.**Abstract**Many assays have been developed to assess anxiety-like behavior. Tests such as the elevatedplus maze (EPM) and open field test (OFT) both assess approach-avoidance behavior in rodents(Gencturk & Unal, 2024). Rodents who spend less time in the more exposed open arms (EPM) orcenter (OFT) are considered to exhibit more anxiety-like behavior. However, we are coming tounderstand that these tests may not be interchangeable and instead may measure divergentbehavioral features of anxiety (Cerqueira et al., 2023). As such, it is important to consider testingrodents in multiple paradigms when attempting to classify them into phenotypes such as high-anxiety or low-anxiety groups. Such phenotyping seeks to identify trait anxiety, a measure ofindividual predisposition towards anxiety which could lead to vulnerability to stress (Weger &Sandi, 2018); trait anxiety should remain stable over time. Thus, it is critical to investigate howrodent behavior changes with repeated testing in these behavioral assays. In male SpragueDawley rats, a second exposure to the EPM resulted in rats spending less time in the open arms(Dawson et al., 1994). In male Wistar rats, those classified as "low grooming" nonetheless groomed more upon a second exposure to the apparatus, while the high groomers exhibitedconsistent levels of grooming. The effects of repeated testing may not be limited to exposure tothe same apparatus. In male mice, experience with other behavioral tests reduced the time andentries into the open arms of the EPM (Shoji & Miyakawa, 2021). This study sought to extend thisprior work to investigate the effects of repeated testing of anxiety-like behavior in adult femaleSprague Dawley rats. We found that, in 10 females, there were no group level changes in groomingpercentage in either the OFT or EPM. Similarly, neither the number of entries into the center (OFT)nor open arms (EPM) changed between trails 1 and 2. While this could suggest that thesemeasures remain consistent across trials, we noted that the relative ranking of rats between trialsoften changed. We found no correlation between trial 1 and trial 2 center entries or open armentries. Thus, additional work is necessary to determine if a combination of behavioral features onmultiple behavioral assays can be used to categorize female rats into high- or low-anxietyphenotypes in a robust manner that remains consistent across multiple trials.

Disclosures: D.M. Rodriguez: None. **P. Gonzales:** None. **S. Osman:** None. **K. Emery:** None. **A.G. Gibson:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.07/II18

Topic: H.03. Motivation

Title: Measuring Trait Anxiety Across Multiple Behavioral Paradigms

Authors: *C. MALLORY[1], R. CORDOVA[4], M. JONES[1], D. RODRIGUEZ[1], G. MERGHANI[1,2], K. EMERY[3];
[2]Neurosci., [3]Psychology and Neurosci., [1]Regis Univ., Denver, CO; [4]Regis Unversity, Denver, CO

Abstract: Trait anxiety is an individual organism's genetic predisposition toward anxiety, which can shape stress responses to adverse stimuli (Weger and Sandi, 2018). In rodent models, trait anxiety is commonly assessed through exploratory behavior in novel or mildly threatening environments; high-anxiety animals usually avoid open spaces, while low-anxiety animals will explore more freely (Shoji and Miyakawa, 2021). Three of the most widely used behavioral paradigms for measuring trait anxiety are the elevated plus maze (EPM), open field test (OFT), and light/dark box (LD). The elevated plus maze (EPM) is a well-established method for classifying trait anxiety, with high-anxiety rodents spending little time in the open arms and low-anxiety rodents spending more time in the open arms. Corticosterone (CORT) is elevated in animals who spend less time in the open arms of the EPM, supporting the construct validity of the EPM as a measure of anxiety. Additionally, CORT is also elevated in both high grooming animals in the EPM and animals who show higher numbers of stretch-attends, which are often interpreted as risk assessment behavior (Rogers, 1999), however these measures are often overlooked in anxiety phenotyping (Walf and Frye, 2007) (Landgraf and Wigger, 2002). While used less commonly for specifically phenotyping trait anxiety, the OFT and LD box are also commonly used as anxiety measures. It is unclear if all these paradigms measure the same construct and which specific measures within the tests most consistently characterize trait anxiety. Behavioral classifications of male and female rats were examined across all three tests using correlation analyses, heat maps, and principal component analysis (PCA). Results suggest that EPM shows strong within-test convergent validity, while inconsistencies between OFT and EPM phenotyping indicate that OFT may better assess exploratory behavior, rather than anxiety, and the LD shows little significant correlation with either of the other tests. PCA further identified three distinct phenotypic groups, one of which appears to show consistent "high-anxiety" behaviors and a second that exhibits an exploratory phenotype. For example, our findings suggest that grooming time in both EPM and OFT converge the most with open arm exploration time in the EPM, meaning grooming may be a reliable indicator of trait anxiety across multiple tests. Here, we seek to propose a specific set of behaviors that can be used to consistently phenotype trait anxiety in rats.

Disclosures: C. Mallory: None. **R. Cordova:** None. **M. Jones:** None. **D. Rodriguez:** None. **G. Merghani:** None. **K. Emery:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.08/II19

Topic: H.03. Motivation

Support: Nu Rho Psi Undergraduate Research Grant

Title: Does trait-anxiety influence the valence of CeA activation?

Authors: *E. YEVARA[1], B. PETRIE[1], R. HILLS[1], R. CORDOVA[1], P. HINSON[2], J. CHATHA[1], G. MERGHANI[2], K. EMERY[2];
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Abstract: Traditionally, the central amygdala (CeA), a subnucleus of the extended amygdala, has been primarily linked to stress and within opponent process theories of addiction, drives withdrawal and promotes relapse via negative reinforcement mechanisms (Koob, 1999). In these models, individuals are motivated to use drugs to alleviate distress associated with withdrawal. However, CeA plays a critical role in integrating emotional and motivational signals that guide behavior in response to stressful and rewarding stimuli without requiring anxiety or distress (Warlow, 2020). Under certain conditions, CeA activation has been shown to facilitate reward-seeking behaviors - even toward harmful stimuli - highlighting its involvement in both aversive and appetitive states (Warlow, 2017). Variability in traits such as anxiety shape how extended amygdala activity influences behavior, and these traits can function as well-established predictors of addiction vulnerability and fundamentally alter how reward and stress circuits are engaged (Baumgartner 2022, Kabbaj 2000). Trait anxiety has been shown to modulate behavioral responses to stress and reward cues, which may alter the valence of CeA engagement. For example, in the ventral tegmental area (VTA), CRF receptor engagement produces opposing effects on motivation in high- and low-anxiety phenotypes, which could be similarly applicable to the CeA (Zalachoras et al., 2022). Given the valence function of the CeA, it is plausible that CeA activation itself might have trait anxiety-dependent effects on incentive salience or aversive processing behavior- similar to those observed in the VTA (Zalachoras et al., 2022). It remains unclear how trait anxiety directly modulates the motivational and affective valence of CeA activation. To test this, male and female rats will be classified as high-anxiety (HA) or low-anxiety (LA) using the elevated plus maze. We will then use chemogenetics to selectively activate the CeA and assess its motivational valence in a conditioned place preference (CPP) paradigm. We hypothesize that CeA activation will be rewarding in LA rats, producing a conditioned place preference, but aversive in HA rats, producing a conditioned place avoidance. These findings would reveal whether individual differences in trait anxiety fundamentally bias the emotional output of the central amygdala. Demonstrating that the same neuronal manipulation can produce opposite emotional states would reshape our understanding of amygdala function and help explain why some individuals are more susceptible to stress-related disorders.

Disclosures: E. Yevara: None. **B. Petrie:** None. **R. Hills:** None. **R. Cordova:** None. **P. Hinson:** None. **J. Chatha:** None. **G. Merghani:** None. **K. Emery:** None.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.09/II20

Topic: H.03. Motivation

Title: Molecularly-resolved and antagonistic serotonergic subcircuits implement fast bidirectional control of stress-coping

Authors: M. PAVLOVIC[1], H. SHI[2], T. ATHEY[4], C. PARKIN[5], J. T. VOGELSTEIN[6], B. MILLER[7], C. M. LISTON[8], L. E. FENNO[9], X. WANG[3], K. DEISSEROTH[10], *M. WRIGHT[1]; [1]Stanford, Stanford, CA; [2]Xiao Wang Lab., [3]Broad Inst., Cambridge, MA; [4]Electrical Engin. and Computer Sci., MIT, CAMBRIDGE, MA; [5]Columbia, New York, NY; [6]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [7]Columbia Univ., new york, NY; [8]Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [9]Psychiatry & Neurosci., Univ. of Texas at Austin, Austin, TX; [10]Stanford Univ., Stanford, CA

Abstract: Maladaptive stress-coping behaviors are a hallmark of mood disorders, yet most treatments operate on the timescale of weeks and the neural populations capable of rapidly modulating these behaviors remain unknown. The dorsal raphe nucleus (DRN) is a central node for stress regulation and the principal source of forebrain-projecting serotonin (5-HT), but its internal circuit organization and the functional roles of DRN cell-types in controlling stress-coping remain unclear. Here, we dissect the molecular and functional architecture of DRN subcircuits by integrating spatial transcriptomics, optogenetics, and whole-brain circuit mapping to define a molecular logic for rapid serotonergic control of stress coping. We identify two transcriptionally distinct 5-HT subtypes—5-HT/Vglut3 and 5-HT/Gad2—that exert opposing effects on stress-coping: activation of 5-HT/Gad2 neurons suppresses coping, while activation of 5-HT/Vglut3 neurons promotes active coping. These subtypes also differ in reinforcement properties, projection fields, local input connectivity, and expression of neuromodulatory receptors suggesting the operation of molecularly distinct antagonistic 5-HT subcircuits. Notably, we also find that 5-HT/Gad2 neurons provide dense local input to 5-HT/Vglut3 neurons, suggesting an antagonistic intra-DRN microcircuit. Our findings reveal a molecularly specified architecture for rapid bidirectional control of stress-coping responses within the DRN, and suggest novel targets for fast-acting subtype-specific serotonergic modulation in the treatment of affective and stress-related disorders.

Disclosures: M. Pavlovic: None. **H. Shi:** None. **T. Athey:** None. **C. Parkin:** None. **J.T. Vogelstein:** None. **B. Miller:** None. **C.M. Liston:** None. **L.E. Fenno:** None. **X. Wang:** None. **K. Deisseroth:** A. Employment/Salary (full or part-time):; Professor, Stanford University. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics. F. Consulting Fees (e.g., advisory boards); Stellaromics, Maplight Therapeutics, Modulight, Allen Institute, RedTree. **M. Wright:** A. Employment/Salary (full or part-time):; Assistant Professor, Stanford University.

Poster

PSTR240: Aversive Learning, Safety Signals, and Defensive Behavior

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR240.10/II21

Topic: H.03. Motivation

Title: Atypical Defensive Responses to Looming Visual Threats in the Autism-Relevant C58/J Mouse Model

Authors: *J. LOPEZ BELLO[1], O. R. HERNANDEZ PEREZ[2], V. S. HERNANDEZ[3];
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Abstract: Autism Spectrum Disorder (ASD) is associated with atypical sensory processing and altered responses to environmental threats. The C58/J mouse strain exhibits behavioral characteristics relevant to ASD, including increased repetitive behaviors, hyperactivity, and alterations in social and sensory responses. To determine whether innate visual threat processing is also altered in this model, we evaluated defensive behaviors using the looming paradigm, a validated assay that mimics the approach of an aerial predator.Behavioral responses of C58/J and C57BL/6J mice were compared by measuring response latency, exploratory rearing, number of entries into a shelter, freezing behavior, and time spent in the shelter following presentation of the looming stimulus. Relative to C57BL/6J mice, C58/J mice showed a trend toward increased exploratory rearing and a greater number of entries into the hideout, as well as a tendency toward reduced latency to enter the hideout. However, significant differences emerged in defensive coping strategies. C58/J mice spent significantly less time in the shelter after stimulus presentation and exhibited significantly greater freezing behavior than C57BL/6J controls.In the looming paradigm, freezing and escape represent alternative innate defensive responses selected according to perceived threat intensity and environmental context. The increased freezing displayed by C58/J mice, together with their reduced shelter-seeking behavior, suggests an altered balance between active and passive defensive strategies. Rather than engaging in goal-directed escape, C58/J mice preferentially adopted a prolonged immobility response when confronted with an overhead visual threat.These findings indicate that although visual threat detection appears to remain largely intact in C58/J mice, the downstream selection of defensive behaviors is altered. The results support the hypothesis that ASD-related phenotypes involve modifications in neural circuits responsible for threat evaluation and behavioral adaptation, highlighting the looming test as a valuable tool for investigating sensory-threat processing and innate defensive behaviors in autism-relevant mouse models.

Disclosures: J. Lopez Bello: None. **O.R. Hernandez Perez:** None. **V.S. Hernandez:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.01/II22

Topic: H.05. Mood Disorders

Support: MSCRF Launch 2026 (RS)
BBRF 25465 (RS)
NIH Grant P50MH136297

Title: Attenuated CaV1.2 - BK Channel Interaction as a Molecular Signature of Mood Switching in Bipolar Disorder: Implications for Precision Medicine

Authors: *R. SRIVASTAVA[1,2], K. ISHIZUKA[1,2], N. GENDUSO[1,2], F. GOES[1,2], M. B. JOHNY[5], T. KARIGO[6], A. SAWA[1,2,3,4,7];
[2]Psychiatry, [3]Neuroscience; Physiology, Pharmacology, and Therapeut., [4]Biomed. Engineering; Genet. Med., [1]Johns Hopkins Univ., Baltimore, MD; [5]Physiol. and Cell. Biophysics, Columbia Univ., New York, NY; [6]Neurosci., Johns Hopkins Univ. / KKI, Baltimore, MD; [7]Mental Hlth., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD

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 approach or a back translation. In the present study, we uncover a novel mechanism that is likely to underlie mood switch, the fundamental phenotype and a major determinant of disease trajectory of bipolar disorder (BP). We initiated the study by looking for a cellular phenotype that significantly correlates with a clinical feature. Given that calcium signaling deficits have been reported in BP, we examined whether and how the deficits exist in our experimental setting, excitatory induced neuronal (iN) cells. We observed slower kinetics in the neuronal activity-dependent calcium signaling (delayed time to peak) in BP compared with healthy controls (HC). Notably, these deficits were significantly correlated with the number of manic episodes, indicating the pathology associated with mood/behavior switch. After this clinico-cellular discovery, we investigated a mechanism underlying the deficits and underscored that the attenuated interaction between voltage-gated calcium channel CaV1.2 and calcium-potential activated big potassium (BK) channel plays a pivotal role for the deficits. The observations were replicated and further characterized in induced pluripotent stem cells (iPSC)-derived excitatory cortical neurons. In the postmortem brains, the CaV1.2-BK protein interaction was also attenuated in BP patients compared with HCs. We further generated a hybrid fusion protein that modulates CaV1.2-BK interaction (novel molecular device) and rescued the BP cellular phenotypes, demonstrating the causal mechanism. Furthermore, we confirmed that the partial knockdown of BK channel resulted in the same calcium kinetic deficits in BP neurons. The BK channel agonists unoprostone and BMS204352 ameliorated the deficits. To address the question of how the cellular deficits impact behavior *in vivo*, we used heterozygote BK knockout (KO) mice. Notably, BK haploinsufficiency combined with mild sleep deprivation displayed a 'behavior switch' in two adaptive behavioral paradigms. The BK channel agonists also ameliorated the behavioral deficits involving the switch. Altogether, we report the attenuated CaV1.2-BK channel interaction in BP and propose that this specific molecular mechanism underlies calcium kinetic deficits and susceptibility to mood switch in a subset of BP patients. This mechanism provides a foundation for establishing a mechanism-driven biomarker and treatment strategy in a precision medicine framework.

Disclosures: R. Srivastava: F. Consulting Fees (e.g., advisory boards); Dainippon Sumitomo Pharma. **K. Ishizuka:** None. **N. Genduso:** None. **F. Goes:** None. **M.B. Johny:** None. **T. Karigo:** 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. F. Consulting Fees (e.g., advisory boards); Dainippon Sumitomo Pharma.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.02/II23

Topic: H.05. Mood Disorders

Title: Abstinence from Substance Use is Associated with Improved TMS Treatment Outcomes

Authors: *K. HUR[1], H. KIM[1], M. COYLE[2], P. GANESH[2], J. C. BROWN[1];
[1]Harvard Med. Sch. / McLean Hosp., Belmont, MA; [2]McLean Hosp., Belmont, MA

Abstract: Substance use is often considered to adversely affect response to repetitive transcranial magnetic stimulation (rTMS), leading to the exclusion of individuals with substance use histories from treatment or recommendations for abstinence during the treatment course. However, empirical evidence supporting these practices remains limited, contributing to a lack of standardized recommendations. This study evaluated whether recent substance use (within one month prior to treatment), use frequency, and abstinence during treatment were associated with clinical outcomes following rTMS. Changes in psychiatric symptoms were assessed using the Behavior and Symptom Identification Scale (BASIS) before, during, and after rTMS treatment. Patients were categorized according to substance use history into alcohol (ALC, n = 184), cannabis (CAN, n = 69), and combined alcohol and cannabis (ALC+CAN, n = 76), with individuals without a history of substance use serving as controls (n = 378). Statistical analyses used linear mixed-effects models ($p < 0.05$). Changes in BASIS scores following rTMS did not differ between controls and ALC ($p = 0.99$) or CAN ($p = 0.48$) groups, whereas the ALC+CAN group showed greater reduction compared with controls ($p < 0.01$). Analysis within each substance use group indicated that substance use frequency was not significantly associated with rTMS-related treatment response across the ALC ($p = 0.22$), CAN ($p = 0.52$), or ALC+CAN ($p = 0.57$) groups. Abstinence during rTMS treatment was significantly associated with greater improvement in BASIS scores in the CAN ($p < 0.001$) and the ALC+CAN groups ($p < 0.001$), with a similar but non-significant trend in ALC group ($p = 0.14$). These findings suggest that a history of alcohol and/or cannabis use does not attenuate the therapeutic effects of rTMS and should not be considered a contraindication for rTMS treatment. Moreover, substance use frequency was not significantly associated with treatment outcomes. Notably, abstinence during treatment was associated with greater clinical improvement, supporting the recommendation of abstinence during the course of rTMS treatment.

Disclosures: K. Hur: None. **H. Kim:** None. **M. Coyle:** None. **P. Ganesh:** None. **J.C. Brown:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.03/II24

Topic: H.05. Mood Disorders

Support: R01MH133561
R01AG080790
R01AG076949

Title: Human Brain and Blood: Shared mitochondrial Biomarkers for Major Depressive Disorder

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Abstract: Major Depressive Disorder (MDD) is a severe psychiatric condition characterized by heterogeneous molecular alterations across brain regions. Increasing evidence highlights mitochondrial dysfunction as a central feature of MDD pathophysiology. **METHODS:** We integrated region-specific bulk transcriptomics datasets comparing MDD and control dorsolateral, orbitofrontal, and anterior cingulate cortex, nucleus accumbens, subiculum, insula, amygdala, and blood samples, to identify mitochondrial dysregulation signatures of MDD using MitoCarta3.0 mitochondrial gene database. We further examined protein-protein interaction (PPI) networks, genome-wide association study (GWAS) risk genes for MDD, and mitochondria pathway-level alterations, focusing on mitochondrial translation and oxidative phosphorylation (OXPHOS). **RESULTS:** We found that 15-20% of the differentially expressed genes (DEGs) identified by those studies were mitochondrial-related and were predominantly upregulated. Integration of blood and brain transcriptomics results revealed that 148 genes were dysregulated in both. Mitochondria-pathway analysis demonstrated that these shared genes are primarily involved in mitochondrial organization, translation, and OXPHOS. PPI network analysis identified 16 hub genes showing concordant up-regulation in brain and blood, including *COX*, ubiquinol-cytochrome c reductase, and *NDUF* gene family, involved in the mitochondrial electron transport chain (ETC). Furthermore, integration of GWAS risk genes with shared mitochondrial DEGs, identified seven genes with gene variants associated with MDD, including *SLC25A37, SLC25A46, MRPL22, TRMT10C, MSRA,* and *HINT1*, which are related to mitochondrial translation, mitochondrial gene expression, mitochondrial RNA modification, mitochondrial tRNA processing, and mitochondrial localization. Additionally, drug enrichment analysis using DSigDB identified compounds that target the shared DEGs. *MSRA* encodes methionine sulfoxide reductase A, an enzyme that reduces methionine sulfoxide to methionine and repairs oxidatively damaged proteins. Further, 3D structure-prediction of protein *MSRA* revealed favorable interactions with candidate compounds, supporting its potential as a therapeutic target in MDD. **CONCLUSIONS:** Overall, our findings suggest that MDD is

characterized by interconnected dysregulation of mitochondrial metabolism, oxidative stress, and translation, which are shared in brain and blood, suggesting these pathways could be biomarkers for MDD or an MDD subtype, and have potential implications for biomarker development and targeted therapies.

Disclosures: R. Mishra: None. **M. Boldrini:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.04/II25

Topic: H.05. Mood Disorders

Title: Functional connectivity using source-localized QEEGt reveals a dose-dependent neuroplastogen signature for Elunetirom, a CNS thyroid hormone receptor agonist prodrug, in the absence of spectral power changes in healthy participants.

Authors: *M. METEA[1], J. HARRIS[2], J. BACCEI[2], W. STRATTON[2], T. SCANLAN[3], G. DAVAR[2];
[1]Lucerum, Inc., Mattapoisett, MA; [2]Autobahn Therapeutics, Inc, San Diego, CA; [3]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Background: Quantitative EEG tomography (qEEGt) enables the localization of neuronal generators, providing biomarkers of postsynaptic activation and network connectivity. Given that psychiatric and neurodegenerative disorders underlie functional dysconnectivity, qEEGt is uniquely suited to assess neuroplastogen efficacy based on functional connectivity (FC), even in the absence of conventional scalp-level spectral changes in EEG. We utilized swLORETA qEEGt to investigate the neuroplastic effects of elunetirom, an investigational, oral CNS-targeted thyroid hormone receptor agonist being evaluated for major depressive disorder (MDD) and bipolar depression (BD). **Methods:** Eighteen subjects across three groups received once-daily oral elunetirom (2.8, 5.6 µg) or placebo (PBO). 19-channel resting-state EEGs were recorded pre-dose ("Pre") and 4 hours post-dose ("Post" at Tmax) on Days 1, 7, and 14 (Eyes Open/Closed). Nonparametric statistics (LucerumKey platform) compared frequency-specific changes in Current Source Density (CSD) Power and FC between elunetirom groups vs. PBO for each Day, assessing progressive effects both on-drug, as well as persistent changes. FC was assessed via Composite Phase Slope Index (cPSI) and changes within Intrinsic Connectivity Networks (ICNs). **Results:** Changes in CSD Power were limited or transient. In contrast, persistent changes occurred in FC (cPSI) globally across brain areas and frequencies. Both "Pre" (Days 7, 14) and "Post" (Days 1, 7, 14) cPSI increased up to 75% (Post) and 50% (Pre). This indicates a widespread neuroplastic effect persisting between doses. A dose- and time-dependent relationship was noted, peaking at 5.6 µg on Day 14, confirming stability of neuroplasticity. FC changes specific to ICNs were minimal and sporadic. Taken together, these data suggest synaptic remodeling while maintaining the integrity of specialized cognitive ensembles. **Conclusion:**

Elunetirom was associated with persistent, dose- and time-dependent shifts in global functional connectivity (FC), without observed changes in spectral power. These findings are being further evaluated in the context of preclinical data exploring potential relationships with cerebral bioenergetics and neuroplasticity. Elunetirom's mechanism of action differs from traditional monoaminergic approaches, and its pharmacological profile continues to be studied in patients with MDD and BD.

Disclosures: M. Metea: None. **J. Harris:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Inc. **J. Baccei:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Inc. **W. Stratton:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Inc. **T. Scanlan:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Inc. Other; Founder of and advisor to Autobahn Therapeutics. **G. Davar:** A. Employment/Salary (full or part-time):; Autobahn Therapeutics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Autobahn Therapeutics, Inc.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.05/II26

Topic: H.05. Mood Disorders

Support: Brain & Behavior Research Foundation (Independent Investigator Award)
Depressive and Bipolar Alternative Treatment Foundation
Institute for Mental Health Research
Braun Foundation
Barry and Jane Lang
Arch and Laura Brown
Undergraduate Research Opportunities Program (UROP) Team Grant

Title: Positive affect scores assessed during infrared whole-body hyperthermia predict antidepressant response in participants with major depressive disorder

Authors: *J. D. MARQUEZ[1], J. B. MATHER[2], A. E. MASON[3], S. P. COLE[4], C. L. RAISON[5], C. A. LOWRY[1];
[1]Integrative Physiol., Univ. of Colorado Boulder, Boulder, CO; [2]Vail Hlth. Behavioral

Innovation Ctr., Vail Hlth., Vail, CO; [3]Osher Ctr. for Integrative Hlth., Univ. of California, San Francisco, CA; [4]Res. Design Associates Inc, Yorktown Heights, NY; [5]Psychiatry, Sch. of Med. and Publ. Health, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Current pharmacological treatments for major depressive disorder (MDD) suffer from significant limitations, including major side effects and delayed onset of action, highlighting a need for novel therapeutic strategies. Infrared whole-body hyperthermia (WBH) has emerged as a promising and rapid-acting antidepressant intervention with minimal side effects. A randomized, double-blind, sham-controlled study demonstrated that a single WBH session reduced 17-item Hamilton Depression Rating Scale (HDRS) scores in adults with MDD assessed 1, 2, 4, and 6 weeks post-intervention [Janssen et al., 2016, *JAMA Psychiatry*, 73(8), 789-795]. Identifying early predictors of antidepressant response to WBH may elucidate who will respond and who will not respond to the intervention, which is critical for its clinical implementation. Positive affect (PA) scores derived from the Positive and Negative Affect Schedule (PANAS) were assessed at: P1) baseline, assessed immediately before the device was turned on; P2) immediately after heat lamps were turned off; P3) 1 h after heat lamps were turned off; and P4) 2 h after heat lamps were turned off. We hypothesized that: 1) the maximum PA score (PAMax) assessed across P2, P3, and P4; and 2) the difference between PAMax and baseline (PAΔ) score, would predict subsequent antidepressant response. We conducted an analysis of data from medically healthy adults with MDD who were not on antidepressants (n = 28; 19 female, 9 male; mean ± SD baseline HDRS = 22.3 ± 4.1) and who were randomized to a single session of WBH (n = 14) or sham treatment (n = 14); we did not assess sex differences. Raters blinded to group assignment assessed depression severity using the HDRS at baseline and at 1, 2, 4, and 6 weeks post-intervention. We evaluated associations between PAMax and PAΔ and the longitudinal HDRS outcomes using Linear Mixed Models (LMMs) that accounted for repeated measures and random effects. We evaluated associations between PAMax and HDRS outcomes across the six-week follow-up period using partial correlation analysis. LMM analysis revealed that PAMax scores predicted the subsequent antidepressant response across the six-week follow-up period (p = 0.037). Partial correlations adjusted for baseline HDRS scores revealed that PAMax was correlated with HDRS scores at weeks 2 (p = 0.043) and 4 (p = 0.019). There was a non-significant trend for the LMM association between PAΔ and HDRS scores (p = 0.095). These findings identify PAMax during WBH as an early predictor of antidepressant response, potentially allowing for the identification of likely responders at the time of treatment and usefulness of WBH as a therapeutic strategy for MDD.

Disclosures: J.D. Marquez: None. **J.B. Mather:** None. **A.E. Mason:** 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.; Tiny Blue Dot Foundation, William H. Donner Foundation, Tiny Foundation, Dalio Foundation, Vail Health Foundation, National Institutes of Health, U.S. Department of Defense via the Medical Technology Enterprise Consortium. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EVOLVE Global. F. Consulting Fees (e.g., advisory boards); Oura Health, EVOLVE Global. **S.P. Cole:** None. **C.L. Raison:** 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.; Tiny Blue Dot Foundation, ARPA-H, Vail Health

Foundation. F. Consulting Fees (e.g., advisory boards); Usona Institute, Otsuka, Eli Lilly, AbbVie. **C.A. Lowry:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Kioga, Inc.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.06/II27

Topic: H.05. Mood Disorders

Title: Ropanicant (SUVN-911), an α4β2 nAChR Antagonist: A Phase-2b, Randomized, Double-blind, Placebo-controlled, Parallel-group Study, Evaluating the Efficacy and Safety of Ropanicant in Patients with Major Depressive Disorder

Authors: *V. PALACHARLA, A. MOHAMMED, V. BENADE, S. JETTA, V. GOYAL, R. SUBRAMANIAN, S. PANDEY, I. KALAIKADHIBAN, D. DOGIPARTI, P. JAYARAJAN, A. K. SHINDE, R. NIROGI, V. JASTI;
Suven Life Sci. Ltd, Hyderabad, India

Abstract: Ropanicant (SUVN-911) is a potent and selective α4β2 nicotinic acetylcholine receptor (nAChR) antagonist and has demonstrated more than 100 fold selectivity. Ropanicant showed good oral bioavailability in preclinical species. Good oral exposures and increased cortical serotonin and norepinephrine levels translated into robust antidepressant like effects in animal models. It showed faster onset of antidepressant activity, procognitive activity, and did not induce sexual dysfunctions in animal models thus, addresses major limitations of the currently used antidepressants. Non-clinical safety of ropanicant has been established in battery of safety pharmacology, general toxicity, embryo-fetal developmental and genotoxicity studies. An open-label parallel-group Phase-2a study evaluated the safety and efficacy of Ropanicant in patients with moderate to severe MDD patients across multiple centers in the USA (NCT06126497). A total of 41 patients were randomized to receive Ropanicant either 45 mg qd, 30 mg twice a day (bid), or 45 mg bid in a ratio of 1:1:1, for duration of 14 days. Of the 41 randomized patients, 14 received Ropanicant 45 mg qd, 14 received 30 mg bid, and 13 received 45 mg bid. Day 14 MADRS total score showed a statistically significant improvement from baseline ($p < 0.0001$) across Ropanicant treatment arms. Ropanicant was found to be safe and well tolerated in patients with moderate to severe MDD across tested doses. Currently, a Phase-2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial is ongoing (NCT06836063). The study is evaluating the efficacy and safety of two Ropanicant doses compared to placebo. The primary objective of the study was to evaluate the efficacy of Ropanicant compared to placebo in reducing the depressive symptoms. The secondary objectives were efficacy of ropanicant compared to placebo based on clinician reported outcome, functional impairment, and safety. The primary endpoint was the change from baseline in MADRS total score at Day 43 (Week 6). The study was planned to randomize 195 patients in a 1:1:1 ratio to receive dose 1 and dose 2 of Ropanicant bid or placebo bid (65 per treatment group) for a

duration of 6 weeks. Study has completed the recruitment and topline data readout is expected in H2 2026. The demographics and baseline characteristics are consistent with other MDD studies and are representative of MDD population. The results from the double-blind, randomized, placebo-controlled Phase-2b clinical study will inform the clinical utility of Ropanicant.

Disclosures: V. Palacharla: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **I. Kalaikadhiban:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **D. Dogiparti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A.K. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.07/II28

Topic: H.05. Mood Disorders

Support: SECIHTI CF-2023-I-1259

Title: Efficacy of Accelerated Continuous Theta Burst Stimulation in the Treatment of Severe, Moderate, and Mild Depressive Symptoms: A Preliminary Data Set

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Abstract: Depression refers to a complex array of symptoms that lead to disturbances in mood, including sadness, feelings of emptiness, diminished pleasure in daily activities, and irritable mood, accompanied by somatic and cognitive changes that affect the individual's daily functionality. Transcranial magnetic stimulation (TMS) is a promising noninvasive treatment for depressive symptoms. Due to growing evidence of the benefits of TMS protocols for various neurological and psychiatric disorders, in this study, we explore the impact of subthreshold continuous theta burst stimulation (cTBS) over the right dorsolateral prefrontal cortex (dlPFC) in the treatment of depressive symptoms. cTBS was applied to the dlPFC for 5 minutes twice a day, with a 1-hour interval, for 10 days (a total of 20 sessions). Participants were either categorized into severe or moderate symptoms, then further randomised into either cTBS or sham. Symptoms

were evaluated using the Beck Depression Inventory (BDI-2) and the Montgomery-Åsberg Depression Rating Scale (MADRS) at 5 time points: pre-intervention (baseline), after stimulation, and at 1, 3, and 6 months later. Participants were divided into four groups: severe cTBS (n=26), severe sham (n=19), moderate/mild cTBS (n=10), and moderate/mild sham (n=5). Our preliminary findings indicate a reduction in depressive symptoms across all conditions, with therapeutic effects being sustained throughout the six-month post-intervention period. Although all conditions exhibited a reduction in depressive symptoms, the effect was more pronounced in the groups that received stimulation. Research on cTBS may help develop faster and more effective treatments for depressive symptoms in certain population groups.

Disclosures: N.M. Kemp: None. **J. Contreras Soria:** None. **G. Rivera-Urbina:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.08/II29

Topic: H.05. Mood Disorders

Support: FTF Foundation
Picower Institute for Learning and Memory
Schmidt Science Fellowship
Anesthesia Initiative Fund.

Title: Spectral Dynamics of Frontal Electroencephalogram During Electroconvulsive Therapy

Authors: *M. S. BREAULT[1], G. KANG[2], S. ORGUC[3], M. AREGAWI[4], B. TSENG[5], M. HENRY[6], R. J. HORVATH[7], S. SEINER[8], E. N. BROWN[9];
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Abstract: Electroconvulsive therapy (ECT) is one of the most effective treatments for treatment-resistant depression (TRD). Yet, the neurophysiological mechanisms underlying this effectiveness remain poorly understood. Prior EEG studies have largely focused on seizure characteristics and postictal generalized EEG suppression (PGES), with comparatively little attention to brain dynamics during anesthetic induction and recovery. This study aims to examine the spectral characteristics across ECT sessions in patients with major depressive disorder and bipolar disorder. We characterized frontal EEG activity across the ECT session in 15 patients undergoing right unilateral or bilateral ECT. Right frontal recordings were segmented into 10-second windows spanning seven treatment stage: baseline, methohexital, pre-ECT, ECT, post-ECT, mid-recovery, and emergence. EEG amplitude and frequency-domain power spectral

densities (PSDs) were compared between adjacent stages using a multitaper bootstrap approach. We observed distinct stage-specific spectral patterns with marked transitions. Anesthetic induction revealed a clear EEG shift from consciousness to unconsciousness. The ictal phase showed broadband power increases across frequencies, followed by a broadband decrease in the postictal phase. Mid-recovery demonstrated partial restoration of power from slow-delta to beta ranges, progressing to increased gamma activity during emergence. Our findings suggest a reproducible sequence of neurophysiological transitions across the entire ECT session. This study provides evidence that structured, reproducible EEG dynamics span the full ECT session and motivates more rigorous use of EEG to improve treatment response.

Disclosures: M.S. Breault: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US 63/707524. **G. Kang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US 63/707524. **S. Orguc:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US 63/707524. **M. Aregawi:** None. **B. Tseng:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US 63/707524. **M. Henry:** None. **R.J. Horvath:** None. **S. Seiner:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PASCALL, US 63/707524.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.09/II30

Topic: H.05. Mood Disorders

Title: Dynamic changes in plasma extracellular vesicle characteristics predict rapid-acting antidepressant response in clinical trials of depression

Authors: *R. ORSO, A. S. FELTRIN, A. M. NOVICK, C. N. EPPERSON, T. L. BALE; Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Major depressive disorder remains one of the leading causes of disability worldwide, and many patients do not respond adequately to traditional antidepressant treatments. Rapid-acting interventions, including ketamine and psilocybin, have recently shown promising effects for treatment-resistant depression, providing an opportunity to identify biomarkers predictive of treatment response. Blood plasma from two recent clinical trials for: 1) open-label IV ketamine (Bio-K) and 2) a randomized controlled pilot trial for psilocybin that demonstrated significant improvements in depressive symptoms, was examined for changes in extracellular vesicle (EVs) characteristics. EVs are circulating nanoparticles important for rapid and specific cell-to-cell communication and systemic immune regulation that hold great potential as predictive

biomarkers of individual treatment response. Here, we investigated longitudinal changes in plasma EV characteristics, including EV concentration and size distribution, and computationally modeled these with acute and durable treatment response. Blood samples were collected before and after ketamine (IV 0.5 mg/kg; NCT03156504) and psilocybin (oral 25 mg; NCT06230757) administration in separate clinical trials. Plasma EVs were isolated using size-exclusion chromatography, and EV concentration and size were quantified using nanoparticle tracking analysis. Response to treatment was determined using the Montgomery-Åsberg Depression Rating Scale (MADRS), with an effective response defined as a ≥50% reduction in MADRS score following treatment. We found that EV concentration and size changes were associated with responder status and next examined these features to estimate probability of treatment response using a Generalized Linear Mixed Model (GLMM). Both ketamine and psilocybin treatment produced a significant increase in secretion of circulating EVs, indicating a measurable physiological EV response following intervention. The GLMM using EV-derived features showed potential to stratify responders and non-responders in both clinical trials and estimate response probability. These findings suggest that relatively direct EV measures may provide clinically relevant information without requiring future molecular cargo profiling or proteomic analyses. Together, these studies support plasma EVs as candidate biomarkers of treatment response in depression. EV-based modeling may offer a scalable approach to improve response prediction in depression, while future studies integrating EV cargo analyses may help define the biological pathways underlying treatment response. ADDIN EN.REFLIST

Disclosures: R. Orso: None. **A. S. Feltrin:** None. **A.M. Novick:** None. **C.N. Epperson:** None. **T.L. Bale:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.10/II31

Topic: H.05. Mood Disorders

Support: CAPES – Financing Code 001
FAPESP 2023/17468-7

Title: CYP2D6 intermediate metabolizer status, fluoxetine phenoconversion, and serotonin toxicity at therapeutic doses: a mechanistic clinical neuropharmacology case series

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Abstract: Introduction Serotonin syndrome, or serotonin toxicity, is a potentially serious adverse drug reaction associated with increased serotonergic activity in the central and peripheral nervous systems. Although classically related to overdose or the combination of multiple

serotonergic agents, interindividual variability in antidepressant metabolism may also contribute to susceptibility to serotonin toxicity during standard pharmacological treatment. We report two consented cases of serotonin toxicity occurring during therapeutic-dose fluoxetine treatment for mood and anxiety symptoms, in which pharmacogenomic testing revealed CYP2D6 intermediate-metabolizer genotypes. **Results Case 1** was a 27-year-old male previously treated with escitalopram and olanzapine, whose regimen was changed to fluoxetine and low-dose haloperidol. After fluoxetine dose escalation from 20 to 40 mg/day, he developed limb tremor, myoclonus, hyperreflexia, tachycardia, and mild confusion. Symptoms improved after fluoxetine discontinuation and diazepam administration. Pharmacogenomic testing identified CYP2D6 *1/*4 and CYP2C19 *1/*2, consistent with intermediate metabolism for both enzymes. **Case 2** was a 30-year-old female with major depressive disorder and generalized anxiety disorder, previously treated with mirtazapine and pregabalin. After switching to fluoxetine, titrated to 40 mg/day, she developed gastrointestinal symptoms, body aches, tachycardia, insomnia, hand tremor, and myoclonus, which resolved after fluoxetine discontinuation. Genotyping showed CYP2D6 *1/*4, compatible with intermediate CYP2D6 metabolism, and CYP2C19 *1/*17, compatible with rapid CYP2C19 metabolism. **Conclusion** Case 1 fulfilled both Sternbach and Hunter criteria, whereas Case 2 fulfilled Sternbach criteria but could not be confirmed by Hunter criteria because clonus or hyperreflexia were not documented. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale yielded a probable relationship in both cases. These findings suggest that CYP2D6 intermediate-metabolizer status may contribute to increased vulnerability to fluoxetine-related serotonin toxicity, particularly during dose escalation and in the context of serotonergic polypharmacy. Integrating pharmacogenomic testing with structured diagnostic criteria and causality assessment may improve recognition of antidepressant-induced serotonin toxicity in patients treated for mood disorders.

Disclosures: L.R. Poian: None. **R. Teixeira de Sousa:** None. **S. Chiavegatto:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.11/II32

Topic: H.05. Mood Disorders

Support: Stanley Family Foundation

Title: Therapeutic Mechanisms of Lithium Treatment for Bipolar Disorder Investigated in Akap11 Mouse Model

Authors: *M. J. Q. CHEN, B. J. SONG, A. J. GRANGER, M. H. SHENG;
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Abstract: Bipolar disorder (BD) roughly affects over 1% of the world population and is a leading cause of disability worldwide, especially among young adults. While there is currently

no perfect cure, lithium has been historically used as mood stabilizer to prevent manic and depressive episodes, and is the gold-standard treatment for BD patients. Despite its wide clinical use, lithium's therapeutic mechanisms remain unclear. Learning its mechanisms of action will both reveal further insights to BD's disease etiology and push progress in the development of more effective and selective therapeutic interventions.
AKAP11, a top risk variant identified in the Bipolar Exomes (BipEx) Project, encodes protein Akap11 that localizes PKA to specific cellular compartments, and interacts with myriad cell signaling and trafficking molecules. In particular, Akap11 binds to and mediates the inhibition of GSK3B, a key therapeutic target of lithium. We previously characterized Akap11 mutant mice as a genetic model for BD, observing various molecular and behavioral phenotypes like synaptic PKA elevation, major transcriptomic impact to the striatum, and mood-star changes that can be induced by stress or amphetamine. Now we leverage this mouse model to study the therapeutic mechanisms of lithium.
Here we present the transcriptomic and behavioral results from Akap11 mutant mice treated with the mood stabilizing compound lithium carbonate. We conducted bulk RNA-seq across multiple brain regions and found that lithium has strong transcriptomic effects across all brain regions. We found a notable correction of synapse-related gene expression deficits in the cortex and basal ganglia. These results will help us understand the mood stabilizing mechanism of lithium, and lay the groundwork for future therapeutic discovery.

Disclosures: M.J.Q. Chen: None. **B.J. Song:** None. **A.J. Granger:** None. **M.H. Sheng:** None.

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PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.12/JJ1

Topic: H.05. Mood Disorders

Support: JSPS KAKENHI 22K21150
JSPS KAKENHI 23K14804

Title: Chemoinformatics prioritization of CMap-derived candidate compounds linked to a brain-enriched extracellular vesicle RNA signature in bipolar disorder

Authors: *Y. KAGEYAMA, Y. DEGUCHI, S. OKURA, E. FUJIKAWA, T. TANAKA, K. INOUE;
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Abstract: Background: Although multiple hypotheses have been proposed for the pathophysiology of bipolar disorder (BD), mechanism-based treatment options remain limited. We previously performed RNA sequencing of blood-derived brain-enriched extracellular vesicles (EVs) from patients with BD and identified a 145-gene signature that differed from healthy controls. Connectivity Map (CMap) analysis nominated compounds that may reverse this

disease-associated transcriptional signature. Here, we applied chemoinformatics to prioritize these candidates by chemical properties, predicted targets, and pathway relevance.
Methods: Candidate drugs were annotated with PubChem identifiers and SMILES, and RDKit was used to calculate physicochemical and drug-likeness features. Predicted targets were obtained using SwissTargetPrediction, while known bioactivity and clinical development information was annotated using ChEMBL. Enrichment analyses were performed for the 145-gene signature and SwissTarget-derived target genes across seven libraries: Gene Ontology, KEGG, Reactome, MSigDB Hallmark, and WikiPathways. Shared pathways were grouped into major disease axes, and compound-level pathway relevance scores were calculated from the overlap between predicted targets and disease-associated pathway axes.
Results: SwissTargetPrediction yielded 93 unique target gene symbols. Pathway comparison showed convergence between the BD EV RNA signature and predicted compound targets across disease-relevant axes, including mitochondrial/oxidative stress, immune-interferon/cytokine signaling, RNA processing/splicing, intracellular signaling/growth factor pathways, cellular homeostasis/stress response, neuronal/synaptic relevance, and chromatin/transcriptional regulation. Integrating pathway relevance with chemoinformatic features, ChEMBL annotations, and candidate classification enabled prioritization of compounds with multi-axis biological connectivity to the disease-associated signature.
Conclusions: This integrative chemoinformatics workflow links CMap-derived candidate compounds to molecular pathways represented in a BD brain-enriched EV RNA signature and provides a scalable framework for prioritizing candidate therapeutics for future network-based and experimental validation.

Disclosures: Y. Kageyama: None. **Y. Deguchi:** None. **S. Okura:** None. **E. Fujikawa:** None. **T. Tanaka:** None. **K. Inoue:** None.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.13/JJ2

Topic: H.05. Mood Disorders

Support: Medical Research Council, UK

Title: Preclinical characterisation of a selective α2/3 $GABA_A$receptor positive allosteric modulator with anxiolytic efficacy and no sedation

Authors: *J. R. ATACK[1], M. O. POPA[1], M. PARADOWSKI[2], G. PHILLIPS[3], J. K. ROWLETT[4], J. J. LAMBERT[3], S. E. WARD[1];
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Abstract: Selective positive allosteric modulators (PAMs) of α2/3-containing $GABA_A$ receptors have been investigated as potential anxiolytics with reduced sedative liability compared with nonselective benzodiazepines. Clinical candidates exhibiting α2/3 selectivity and minimal α1 activity have demonstrated favorable tolerability and signals of efficacy in generalized anxiety disorder, while more recent compounds often incorporate additional α5 activity. Here, we describe the discovery and preclinical characterization of Compound 1, a novel α2/3-selective $GABA_A$ receptor PAM with minimal α1 and α5 activity. Compound 1 was identified through iterative medicinal chemistry optimization and evaluated using human recombinant receptor binding and electrophysiological assays. In vitro microsomal stability and membrane permeability studies supported progression to in vivo pharmacokinetic and CNS target engagement studies, including evaluation of $GABA_A$ receptors occupancy in rodent forebrain. Functional selectivity within the chemical series was further assessed using ex vivo electrophysiological recordings in mouse brain slices. Anxiolytic efficacy was evaluated in the rat elevated plus maze (EPM), while motor and sedative effects were assessed using the rat rotarod assay. Sedative liability was further examined quantitatively in nonhuman primates using standardized behavioral observation categories derived from pediatric anesthesiology classifications. Compound 1 demonstrated potent in vitro potentiation at α2/3-containing $GABA_A$ receptors, with no detectable α1 activity and low α5 activity. Following oral administration in rats, approximately 50% receptor occupancy was achieved at 0.5 mg/kg, corresponding to a plasma EC50 of 52 ng/mL. In the EPM, Compound 1 produced a dose-dependent increase in open-arm exploration, consistent with anxiolytic activity. No motor impairment was observed in the rotarod assay at doses up to 30-fold above the minimum effective anxiolytic dose. In nonhuman primates, Compound 1 produced neither sedation nor ataxia at doses that blocked alprazolam-induced deep sedation, unlike other clinical candidates. These findings demonstrate that selective α2/3 GABAA receptor potentiation can produce robust anxiolytic-like effects while avoiding sedation-related and motor impairment liabilities across rodent and non-human primates.

Disclosures: J.R. Atack: A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. **M.O. Popa:** A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. **M. Paradowski:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics. F. Consulting Fees (e.g., advisory boards); Draig Therapeutics. **G. Phillips:** None. **J.K. Rowlett:** F. Consulting Fees (e.g., advisory boards); Draig Therapeutics. **J.J. Lambert:** F. Consulting Fees (e.g., advisory boards); Draig Therapeutics. **S.E. Ward:** A. Employment/Salary (full or part-time):; Draig Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Draig Therapeutics.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.14/JJ3

Topic: H.05. Mood Disorders

Support: NAP2022-I-4/2022/Magyar Tudományos Akadémia (Hungarian Academy of Sciences)
NAP2022-I-3/2022/Magyar Tudományos Akadémia (Hungarian Academy of Sciences)
NAP2022-I-1/2022/Magyar Tudományos Akadémia (Hungarian Academy of Sciences)
TKP2021-EGA-25/Emberi Erőforrások Minisztériuma (Ministry of Human Capacities)
NKFIH OTKA K146077 (National Research, Development and Innovation Office)
OTKA National Research Excellence program 151425 (National Research, Development and Innovation Office)
Gedeon Richter Excellence PhD Scholarship (Gedeon Richter Talentum Foundation)
NKFIH Richter Grant (National Research, Development and Innovation Office)

Title: RNA-seq reveals coordinated oligodendroglial, mitochondrial, and neuroimmune alterations in the human parahippocampal cortex (PHC) associated with suicide

Authors: *T. HAJDU[1], F. DÓRA[1,2], E. DOBOLYINE RENNER[2], M. PALKOVITS[2], A. DOBOLYI[3,1];
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Abstract: Suicide is associated with dysfunction of large-scale brain networks, particularly the default mode network (DMN). The parahippocampal cortex (PHC), a medial temporal lobe DMN hub, has been implicated in suicidal behavior, yet its molecular pathology remains poorly understood. We therefore characterized transcriptomic alterations in the PHC of suicide decedents. RNA sequencing (RNA-seq) was performed on postmortem PHC samples from 11 suicide decedents and 11 demographically matched controls. Differential expression analysis was conducted using DESeq2, followed by Gene Ontology (GO), KEGG and Reactome pathway enrichment analyses, and STRING protein-protein interaction network analysis. Selected transcripts were validated by quantitative real-time PCR (qRT-PCR). Transcriptomic profiling identified 372 differentially expressed genes (201 upregulated and 171 downregulated; $|\log2 \text{ fold change}| > 1$, adjusted $p < 0.05$). Functional enrichment analyses revealed activation of oligodendrocyte- and myelination-associated pathways. Upregulated genes included gliomedin (GLDN), NIPA-like domain containing 4 (NIPAL4), and plakophilin-1 (PKP1). In contrast, downregulated genes were enriched for oxidative phosphorylation, chemokine signaling, and G protein-coupled receptor pathways. Reduced expression was observed for ATP synthase membrane subunit 6 (MT-ATP6), NADH dehydrogenase subunit 4 (MT-ND4), oxytocin receptor (OXTR), adhesion G protein-coupled receptor G7 (ADGRG7), chemokine C-X-C motif ligand 1 (CXCL1) and ligand 11 (CXCL11). Protein interaction network analysis identified

suppression of mitochondrial respiratory chain components and neuroimmune signaling pathways. Consistent with our previous proteomic findings in the PHC, these data indicate altered mitochondrial bioenergetics in suicide. qRT-PCR validation demonstrated strong concordance with RNA-seq results ($r = 0.86$, $p < 0.0001$), confirming suicide-associated upregulation of oligodendrocyte-related genes (GLDN, NIPAL4, PKP1) and downregulation of mitochondrial (MT-ATP6, MT-ND4) and neuronal receptor genes (OXTR, ADGRG7). These findings define a PHC-specific molecular signature in suicide characterized by enhanced oligodendrocyte-associated transcriptional programs, impaired mitochondrial energy metabolism, reduced receptor-mediated neuronal signaling, and attenuated neuroimmune activity. The results implicate neuronal, oligodendroglial, and neuroimmune dysfunction in the molecular pathology of suicide and identify potential targets for future mechanistic investigations.

Disclosures: T. Hajdu: 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.; Gedeon Richter Excellence PhD Scholarship (Gedeon Richter Talentum Foundation), NKFIH Richter Grant (National Research, Development and Innovation Office). **F. Dóra:** 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.; NKFIH Richter Grant (National Research, Development and Innovation Office). **E. Dobolyine Renner:** None. **M. Palkovits:** None. **A. Dobolyi:** 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.; NKFIH Richter Grant (National Research, Development and Innovation Office).

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.15/JJ4

Topic: H.05. Mood Disorders

Support: R01AG068130

Title: Pharmacological inhibition of GCPII promotes resilience to chronic stress in mice

Authors: *C. RUTLEDGE[1], Y. LI[2], C. TALLON[3], J. ALT[3], X. ZHU[4], B. S. SLUSHER[5]; [1]Biomed. Engin., Johns Hopkins, Baltimore, MD; [2]Dept. of Psychiatry and Behavioral Sci., [3]Johns Hopkins Univ., Baltimore, MD; [4]Psychiatry, JHU, Baltimore, MD; [5]Johns Hopkins Drug Discovery, Baltimore, MD

Abstract: Chronic stress is a major risk factor for depression and other psychiatric disorders, many of which lack adequate treatment. Glutamatergic dysregulation contributes to stress-related disorders, with excess glutamatergic signaling exacerbating stress-induced pathology. Glutamate carboxypeptidase II (GCPII) hydrolyzes the abundant neuropeptide N-acetylaspartylglutamate (NAAG) to generate glutamate. We therefore investigated whether pharmacological inhibition of GCPII promotes resilience to chronic stress, using independent cohorts of mice to assess endocrine and behavioral outcomes. Mice were exposed to chronic social defeat stress (CSDS) and treated with vehicle or 2-(phosphonomethyl)pentanedioic acid (2-PMPA), a GCPII inhibitor. CSDS significantly increased plasma corticosterone and aldosterone levels in vehicle-treated mice relative to non-CSDS controls ($P<0.01$), while 2-PMPA normalized both corticosterone ($P<0.001$) and aldosterone ($P<0.01$) (n=5-6 males/group). CSDS also induced selective social and cognitive deficits (with intact locomotor and anxiety-related behavior) that were attenuated by 2-PMPA (n=7 males/group). 2-PMPA significantly improved recognition memory in the novel object recognition test ($P<0.05$) and social behavior in the social interaction test ($P<0.05$) relative to CSDS vehicle-treated mice. Preliminary CSF measures show a trend toward reduced NAAG in stressed mice consistent with stress-induced GCPII activity (n=3 males/group). Consistent with these findings, chronic 2-PMPA treatment increased median survival from 622 to 721 days ($P<0.05$; hazard ratio for mortality=2.91 for vehicle vs 2-PMPA) in an aging cohort (n=24/group, mixed-sex with no significant sex difference) housed under reduced cage-change frequency, a chronic mild stressor arising from husbandry changes occurring during the COVID pandemic. This survival benefit was absent in cohorts maintained under standard husbandry. Exploratory secondary analyses of publicly available human datasets support involvement of FOLH1/GCPII in stress-related disorders, including significant gene-level association with major depressive disorder ($P<0.02$) and differential GCPII protein abundance in dorsolateral prefrontal cortex of suicide attempters ($P<0.001$) (ROSMAP-derived). These findings demonstrate that GCPII inhibition reduces physiological and behavioral consequences of chronic stress and support GCPII as a regulator of stress susceptibility. Pharmacological inhibition of GCPII may therefore represent a novel therapeutic strategy for promoting resilience to chronic stress and stress-related psychiatric disorders.

Disclosures: C. Rutledge: None. **Y. Li:** None. **C. Tallon:** None. **J. Alt:** None. **X. Zhu:** None. **B.S. Slusher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent WO2025183868A1.

Poster

PSTR241: Mood Disorders: Treatment and Drug Discovery

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR241.17/JJ6

Topic: H.05. Mood Disorders

Support: R01 MH132680
U01 DA053826

P50 MH096889
Bren Foundation

Title: Maladaptive neuropeptide signaling plasticity drives enduring reward deficits after early-life stress

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Abstract: Background: While brain systems mediating acute stress are essential for survival, chronic or early-life stress (ELA) often disrupt the ability to experience pleasure, leading to anhedonia and depression. For decades, the neuropeptide corticotropin-releasing hormone (CRH) system has been a target for treating major depression. However, the repeated failure of clinical trials blocking CRH receptor 1 (CRHR1) has left the therapeutic role of CRH signaling a major unresolved mystery. Here, we uncover the peptide signaling plasticity behind this enigma. Methods: In control and ELA mice, we pair G protein-coupled activation-based (GRAB) imaging for CRHR1 and CRHR2 in the nucleus accumbens (NAc) with pharmacological approaches in response to aversive and appetitive cues. We further utilize MERscope spatial transcriptomics to characterize the expression, colocalization and anatomical organization of the CRH family in the NAc. Results: We demonstrate CRH signaling via CRHR1 indeed disrupts reward behaviors in naïve mice, yet this mechanism becomes permanently dysregulated following ELA, producing an anhedonia-like state. Instead, activating CRH receptor 2 (CRHR2) in adult ELA mice reverses their anhedonia. Conclusions: These findings redefine our understanding of stress-mediated anhedonia and provide a precise, novel therapeutic target for stress-related mental illness.

Disclosures: M.T. Birnie: None. **L. Taniguchi:** None. **L. Harvey:** None. **M. Tetzlaff:** None. **L. Mattioni:** None. **A. Floriou-Servou:** None. **G. Angeles:** None. **Y. Chen:** None. **T.Z. Baram:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.01/JJ8

Topic: H.08. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse Intramural Research Program

Title: Recent substance use and AI attitudes moderate user responses to affective and memory-based chatbot design

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Abstract: Conversational AI is increasingly being explored for mental health and substance-use-related support, yet little is known about how users with recent substance use perceive specific chatbot design features. We examined if associations between recent substance-use history and chatbot user experience differed by response style.
783 participants recruited through social media advertisements were randomized to chatbot conditions at study entry. 491(*M (SD)*age = 31.4 (9) years; 49.5% female; 64.8% White) completed the survey, passed attention checks, and completed more than 10 conversation turns. The 2 × 2 × 2 design crossed affective framing (fact vs. feeling), response pace (human-like vs. no-delay), and response memory (recall vs. stateless), using GPT-4o mini. Participants reported demographics, recent substance use, and AI/technology attitudes, followed by a 10-minute chatbot interaction and post-interaction ratings. Recent substance use was assessed via 3 questions across past-two-week binge drinking, tobacco/nicotine use, and cannabis use; 368 participants (75%) endorsed at least one type, with breadth coded as the number endorsed. As response pace manipulation failed, we focused on remaining two conditions.
In stepwise models, using any substance was linked only with lower perceived ease of learning the chatbot, $b = -0.27$. Greater substance-use breadth predicted lower happiness, $b = -0.12$; engagement, $b = -0.15$; and perceived ease of learning, $b = -0.16$, but not retention. Substance-use breadth also interacted with affective framing for happiness, $b = 0.13$, and engagement, $b = 0.17$, showing that negative associations between breadth and these outcomes were weaker under fact-based than feeling-based framing. AI technology skepticism consistently predicted poorer outcomes and interacted with response memory for happiness, engagement, and task success, suggesting that recall-based responses may have buffered skepticism-related differences. The affective framing × response memory × technology skepticism interaction was significant for happiness in both binary-use, $b = -0.21$, and breadth, $b = -0.20$, models, suggesting that recall-based responses buffered the negative links between technology skepticism and happiness primarily under feeling- not fact-based framing. All ps < 0.03.
Findings suggest that broader recent substance use as is linked to less favorable chatbot experiences, but fact-based framing may reduce these disadvantages for happiness and engagement. Technology skepticism remains a key barrier, underscoring the need to tailor conversational AI to users' substance-use histories and attitudes toward technology.

Disclosures: T. Liu: None. **S. Swargam:** None. **E. Senko:** None. **B. Curtis:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.02/JJ9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant RM1HG011014-02
NIH Grant 1OT2OD026673- 01
NIH Grant DP2HG009623-01
NIH Grant R01HD096770
NIH Grant R35NS097404
Cha Zuckerberg Initiative Grant EOSS-0000000082
Cha Zuckerberg Initiative Grant HCA-A-1704-01895
NIDA Grant P01DA047233
NIDA Grant R01DA014133

Title: A Whole Brain Single Cell Genomic Approach to Elucidating Escalation of Oxycodone Intake

Authors: *N. J. NAKATSUKA[1], C. MCCORMICK[1], B. T. KIPP[3], I. MASCIO[1], L. ARONOV[1], B. W. HUGHES[3], L. JIANG[2], L. WILLS[3], S. CLAYPOOL[4], P. J. KENNY[3], E. J. NESTLER[3], R. SATIJA[1];
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Abstract: Prescription opioids are prescribed widely yet only a small percentage of people escalate their intake towards addiction, and the molecular mechanisms underlying this process are currently unclear. We developed an oral oxycodone procedure where 50 mice were provided a choice between oral oxycodone and water for 21 days and an additional 10 were offered water only. We performed single nucleus RNA sequencing of ~3 million cells across the whole brains of 30 mice (24 oxycodone-exposed and 6 controls; 15 males and 15 females) with enrichment in sequencing for 10 primarily sub-cortical regions previously implicated in reward, opioid biology, and addiction. Similar to humans, oxycodone exposed mice demonstrated a range of escalation of intake, and through unsupervised clustering of intake related factors, we classified oxycodone exposed mice as high escalators (HE) or low escalators (LE), sequencing 12 in each category. We find that HE mice have poorer nest building, consistent with impaired cognitive function. We used a partial least squares regression-based method we recently developed that improves power for differential expression by training on phenotypic variables and uncovering molecular gradients that are correlated with the variables of interest yet more closely aligned to the underlying biology. We find particularly strong transcriptional perturbation in glutamatergic neurons of the dorsal peduncular nucleus associated with preference for oxycodone relative to water, with up-regulation of genes related to synaptic firing. Nucleus accumbens D1 and D2 neurons exhibited strong transcriptional perturbation associated with total oxycodone intake, with up-regulation of genes associated with synaptic stability and ERK output. Astrocytes and oligodendrocytes show compensatory alterations buffering the oxycodone response and supporting the neuronal changes. Overall, the biological pathways we found shed fundamentally new light onto the coordination between cell types and brain regions underlying addiction to opioids.

Disclosures: N.J. Nakatsuka: None. **C. McCormick:** None. **B.T. Kipp:** None. **I. Mascio:** None. **L. Aronov:** None. **B.W. Hughes:** None. **L. Jiang:** None. **L. Wills:** None. **S. Claypool:** None. **P.J. Kenny:** None. **E.J. Nestler:** None. **R. Satija:** E. Ownership Interest (stock, stock

options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neptune Bio. F. Consulting Fees (e.g., advisory boards); Bristol-Myers Squibb, ImmunAI, Resolve Biosciences, Nanostring, 10x Genomics, Neptune Bio, NYC Pandemic Response Lab.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.03/JJ10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH 1ZIADA000638

Title: An exposed-state connectome predicts future compulsive methamphetamine seeking and converges across human relapse, treatment response, and molecular addiction signatures

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Abstract: Relapse is central in substance use disorders, but human brain markers of compulsive drug seeking are difficult to isolate because exposure history, abstinence, and relapse timing are heterogeneous. Rodent self-administration with punishment separates drug exposure from later punishment-resistant seeking. We used rat methamphetamine (METH) self-administration plus footshock to discover an exposure-state connectome predictive of future compulsive seeking, then tested whether this architecture was recoverable in human relapse and treatment-response datasets.Whole-brain resting-state functional connectivity during METH exposure was entered into nested connectome-based predictive modeling to predict a future compulsivity index. The exposed-state connectome predicted later compulsive seeking out of fold (CV $R=0.37$, permutation $p<0.001$). The signed architecture showed broad negative-component burden, with amygdala-related circuitry emerging as a leading module-level carrier.For translation, rat punishment-resistant seeking and human relapse were not treated as identical. Instead, we tested whether the rat-derived signed architecture was recoverable across independent human relapse and treatment-response datasets using homologous connectivity projections at progressively narrower scales. These projections improved relapse classification in pooled cocaine-use-disorder cohorts, with AUCs in the high-0.7 to low-0.8 range beyond demographic models. In independent TMS datasets for cocaine and alcohol use disorders, related projections predicted treatment response or relapse with AUCs ranging from approximately 0.8 to 0.9 and tracked craving improvement with moderate correlations. Gene/protein-interaction analyses further linked CPM-derived genes with addiction-related molecular anchors, supporting molecular-context convergence rather than causal mechanism.These findings suggest that controlled animal models can identify exposure-state connectome architectures difficult to isolate in heterogeneous relapse data. The rat-derived architecture translated not as one identical human score, but as

broad negative/overlap relapse liability, focused amygdala-striatal treatment response, and convergent addiction-related molecular context.

Disclosures: H. Zheng: None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.04/JJ11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIGMS Award Number 5U54GM104942-07

Title: Neural Correlates of Cognitive State Induction During a Smoking-Focused rTMS Intervention

Authors: *A. ISBERG[1], P. KROM[1], M. SMITH[1], H. KOBER[3], V. R. STEELE[4], K. T. LARKIN[1], D. THOMPSON-LAKE[5], J. W. LEWIS[2], M. BLANK[1], U. NAJIB[6], J. J. MAHONEY, III[7], M. V. CHERKASOVA[1];
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Abstract: Background: State dependence of repetitive transcranial magnetic stimulation (rTMS) effects is supported by mechanistic research but is rarely tested in clinical protocols. Although rTMS for cigarette smoking cessation incorporates cue exposure for state induction, this practice is based on limited empirical evidence. We tested the effects of rTMS-concurrent cue-induced craving regulation on subsequent brain activity. Methods: In a within-subjects design, participants with cigarette smoking dependence completed 3 sessions of 20-Hz rTMS targeting the left dorsolateral prefrontal cortex (DLPFC), each paired with a different cognitive state. Craving up- and down-regulation were implemented via the Regulation of Craving (RoC) task, in which participants focused on positive or negative effects of smoking while viewing smoking cues. A control condition involved neutral cue exposure without regulation. Each rTMS session was immediately followed by fMRI including the RoC task (featuring alternating blocks of up-, down-, and no-regulation) and a cigarette Delay Discounting (DD) task. Results: Preliminary data from 8 participants indicate that relative to the control session, rTMS-concurrent up-regulation of craving produces significantly greater activation in the right DLPFC and bilateral posterior parietal cortex during up-regulation blocks (cluster-forming threshold $Z \geq 2.58$; cluster-corrected $p < .05$, FWE). Although no significant differences were observed in DD-related neural activity across conditions, rTMS paired with craving up-regulation significantly increased selection of delayed cigarette rewards ($p = .05$). Data collection is still in progress. Conclusions: rTMS-concurrent up-regulation of craving may amplify the contralateral DLPFC and frontoparietal network engagement typically reported with high-frequency left-DLPFC

stimulation, while also promoting more self-controlled decision-making behaviorally. These preliminary findings support state dependence in addiction-focused rTMS interventions.

Disclosures: A. Isberg: None. **P. Krom:** None. **M. Smith:** None. **H. Kober:** None. **V.R. Steele:** None. **K.T. Larkin:** None. **D. Thompson-Lake:** None. **J.W. Lewis:** None. **M. Blank:** None. **U. Najib:** None. **J.J. Mahoney:** None. **M.V. Cherkasova:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.05/JJ12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA058038

Title: Cross-cultural differences in personality and neurocognitive risk factors for addiction across American, South Korean, and Bulgarian university students

Authors: M. KAKANI[1], E. PSEDERSKA[2,3], M. WHITE[1], K. MCLEAN[1], J. SHIN[4], S. LEE[5], N. SIMEONOVA[3], S. DINOVA[3], M. PITT[6], W.-Y. AHN[4], ***J. VASSILEVA**[1];
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Abstract: Addiction vulnerability is mediated by distinct neurobehavioral pathways, including reinforcement-specific personality and neurocognitive risk profiles, whose expression is moderated by social norms and environmental characteristics across cultures. The goal of this study is to compare neurocognitive and personality risk factors and substance use outcomes, and to identify predictors of alcohol- and drug-related outcomes among college students in the United States (US), South Korea (SK), and Bulgaria (BG). Participants included 97 undergraduate students in the US, 50 students in SK, and 87 students in BG. Neurocognitive risk was indexed with the Monetary Choice Questionnaire (MCQ) measuring delay discounting, a neurobehavioral endophenotype of addiction. Personality risk was assessed with the Substance Use Risk Profile Scale (SURPS), measuring four personality traits (impulsivity, sensation seeking, hopelessness, and anxiety sensitivity) known to increase vulnerability to addiction. Substance use outcomes were measured with the Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT). Significant cross-cultural differences emerged in alcohol use (SK>BG=US), drug use (US>BG=SK), impulsivity (SK>BG=US), and delay discounting (BG=US>SK). Regression analyses with personality and neurocognitive risk factors revealed that the personality traits of impulsivity and anxiety sensitivity were the most robust predictors of both alcohol and drug use in BG. In contrast, delay discounting was a significant predictor of alcohol consumption in SK and impulsivity was a

significant predictor of drug use in the US cohort. Our findings suggest both shared and culture-specific neurobehavioral pathways to substance use vulnerability, with distinct contributions of temporal discounting and personality risk factors across European, North American, and Asian samples. Whereas personality risk pathways appear most robust in European and North American cultures, neurocognitive risk pathways involving temporal discounting of rewards appear more pronounced in South Korea, validating the role of the valuation system in subclinical addiction risk in this population. The findings demonstrate that whereas underlying vulnerabilities to addiction are consistent across diverse populations, their specific behavioral manifestation is heavily influenced by the cultural context. Overall, this study underscores the importance of integrating culture into neurobehavioral models of addiction to refine the identification of global and local risk phenotypes.

Disclosures: M. Kakani: None. **E. Psederska:** None. **M. White:** None. **K. McLean:** None. **J. Shin:** None. **S. Lee:** None. **N. Simeonova:** None. **S. Dinova:** None. **M. Pitt:** None. **W. Ahn:** None. **J. Vassileva:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.06/JJ13

Topic: H.08. Drugs of Abuse and Addiction

Title: Precision functional mapping reveals altered functional connectivity and topography in opioid use disorder

Authors: *M. VERHOEVEN[1,2], N. D. VOLKOW[3], P. MANZA[1,2];
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Abstract: Opioid use disorder (OUD) is characterized by persistent craving, relapse, and high treatment dropout. Neuroimaging shows promise for identifying network-level markers of OUD and recovery, but clinically actionable biomarkers remain limited. This is in part because traditional network analyses assume that all individuals have the same functional topography (i.e., that brain networks occupy the exact same cortical territory across individuals).
We tested whether precision functional mapping (PFM), a method that defines network territories on an individualized basis, improves the sensitivity to detect clinically relevant functional connectivity patterns in OUD. We analyzed identical denoised resting-state fMRI timeseries from male and female adults with OUD in recovery (n=35) and healthy controls (n=39) using both PFM-derived and normative atlas network definitions, focusing on the default mode (DMN), salience (SN), and central executive (CEN) networks. Compared with the atlas approach, PFM enhanced detection of group differences, resulting in a mean gain of 0.153 Fisher-z functional connectivity units (95% CI: 0.118-0.189; bootstrap probability 1.00; one-sided bootstrap $p < 0.001$). PFM also increased clinical association magnitudes within OUD

across 75.4% of tests, with a mean gain of 0.105 Fisher-z functional connectivity units per 1-SD increment relative to the atlas approach (95% CI: 0.099-0.111; bootstrap probability 1.00; one-sided bootstrap $p < 0.001$). The clinical associations with the largest gains from PFM included number of past-month opioid use instances (mean |PFMbeta|-|nonPFMbeta| = 0.164, 95%CI: 0.136-0.193) and OUD treatment duration (mean |PFMbeta|-|nonPFMbeta| = 0.095, 95% CI: 0.036-0.161).
Functional topography analyses showed that individuals with OUD had smaller territorial size of the CEN than controls (18% versus 15% of cortex; $t_{(71)} = 3.75$, $p_{FDR} < .001$, Cohen's $d = 0.77$). This appeared to be driven by OUD participants having significantly greater DMN encroachment into normative CEN territory than controls (OUD versus controls: 10.4% versus 8.7% of DMN encroaching on normative CEN territory; $t_{(71)} = 3.37$, $p_{FDR} = .007$, $d = 0.79$). No other pair of network encroachment showed significant group differences.
Together, these findings suggest that OUD is characterized by altered functional topography across key functional networks. PFM increased sensitivity to detect clinically relevant functional connectivity patterns compared to atlas-based approaches, supporting individualized network mapping as a strategy for identifying biomarkers of OUD dysfunction and recovery.

Disclosures: M. Verhoeven: None. **N.D. Volkow:** None. **P. Manza:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.07/JJ14

Topic: H.08. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse (NIDA), NIH Grant R01DA021421

Title: Affective Symptoms, Decision-Making, and Emotional Inhibitory Control in Recovery from Opioid and Stimulant Use Disorders

Authors: *E. PSEDERSKA[1,2], N. SIMEONOVA[2], S. DINOVA[2], J. L. VASSILEVA[3];
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Abstract: Background: Contemporary neurobiological models of addiction propose that chronic substance use produces persistent neuroadaptations affecting reward processing, cognitive control, and affect regulation. Despite distinct pharmacological mechanisms, both opioid (OUD) and stimulant use disorders (StUD) are associated with affective dysregulation and neurocognitive impairments during recovery. The extent to which affective difficulties and neurocognitive deficits represent convergent or dissociable features of addiction recovery, and whether these patterns differ across substance classes, remains unclear.Methods: Healthy controls (n=37), individuals in recovery from OUD (n=34), and individuals in recovery from StUD (n=56) completed measures of depression, anhedonia, and alexithymia, the Iowa Gambling

Task (IGT), and the Emotional Go/No-Go (EMO GNG) task. Standardized depression, anhedonia and alexithymia scores were combined into a composite affective symptom burden index. Group differences were examined using ANOVA, and general linear models assessed the effects of group, affective symptom burden, and their interaction to decision-making and emotional inhibitory-control performance.Results: Relative to healthy controls, OUD and StUD groups exhibited elevated affective symptom burden, impaired reward-based decision-making, and poorer emotional inhibitory control. Although opioid users demonstrated greater depressive and anhedonic symptoms, both substance-use groups showed comparable impairments in IGT performance and EMO GNG false alarm rates. Affective symptom burden did not account for group differences in decision-making or overall inhibitory-control performance. In contrast, a significant Group × Affective symptom burden interaction emerged for fear-related inhibitory-control errors, with higher affective symptom burden associated with fewer errors in healthy controls, greater errors in opioid users, and no association in stimulant users.Conclusions: Despite differences in affective symptom profiles, opioid and stimulant users exhibited comparable impairments in decision-making and emotional inhibitory control. These findings suggest that neurocognitive dysfunction may represent a transdiagnostic feature of addiction recovery that is only partially related to affective symptom burden, consistent with contemporary models proposing persistent alterations across multiple addiction-relevant neural systems.

Disclosures: E. Psederska: None. **N. Simeonova:** None. **S. Dinova:** None. **J.L. Vassileva:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.08/JJ15

Topic: H.08. Drugs of Abuse and Addiction

Support: Brain & Behavior Research Foundation, NARSAD Young Investigator Award
NIH, DA054339
University of Cincinnati, https://ror.org/01e3m7079, Innovation Award

Title: Reward circuit adaptations after chronic antipsychotic treatment confer addiction vulnerability

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Abstract: Antipsychotics are widely used as a chronic treatment for several psychiatric conditions and off-label indications. Antipsychotics can also alter the brain's reward circuitry, and we recently showed that upon abrupt discontinuation, chronic treatment with the first-generation antipsychotic haloperidol increases cocaine relapse in a rodent model of intravenous

cocaine self-administration. Here, we examined whether this addiction vulnerability behavior translates to both chronic treatment with second-generation antipsychotics and clinical data of patients with substance use disorders (SUD). Adult Long Evans rats (200-250g) received subcutaneous infusions of risperidone, olanzapine, or vehicle for 14 days. Rats were then trained to self-administer intravenous cocaine or oral sucrose pellets for 10 days, with active lever presses paired with cue exposure. Following an extinction period, reward seeking was reinstated via exposure to drug cues for 20 minutes. Dendritic spine morphology and manipulation of MSNs during relapse was quantified using virally labeled D1- and D2-MSNs in the nucleus accumbens core (NAcore). The clinical relationship between chronic antipsychotic use and SUD was assessed using a systematic review of studies that examined the effects of antipsychotic treatment on addictive substance use or craving. In rats, chronic risperidone or olanzapine treatment delayed extinction learning and increased cue-induced cocaine seeking but did not alter the seeking or extinction towards natural reward. Cued relapse increased spine head diameter in NAcore D2-MSNs, but not D1-MSNs after antipsychotic treatment relative to vehicle-treated controls, which was reversed via chemogenic inhibition of D2-MSNs. In patients whose SUDs were treated with antipsychotics, duration of treatment (>4 months) strongly predicted addictive substance use or craving independent of antipsychotic type (first- vs. second-generation) or misused substance (psychostimulant, opioid, alcohol, or cannabis). Chronic antipsychotic treatment, regardless of drug class, was associated with increased vulnerability to addictive substance use and relapse-like behavior in a rat model, which translated to patterns seen in human patients maintained on antipsychotic treatment, with these behaviors being linked to potentiation of D2-MSNs in the ventral striatum.

Disclosures: D. Amato: None. **A. Kruyer:** None. **A. Angelis:** None. **M. Massmann:** None. **C. Waselenko:** None. **A. Tan:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.09/JJ16

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R01DA062540

Title: Cell-Type-Specific Chromatin Remodeling and Transcription Factor Network Disruption in Opioid Use Disorder

Authors: *S. V. SAMBARE[1], M. FISH[3], V. CHERUPALLY[4], B. N. PHAN[5], C. SRINIVASAN[6], J. R. GLAUSIER[8], C. FU[9], D. A. LEWIS[10], A. R. PFENNING[7], M. L. SENEY[11], R. W. LOGAN[2];
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Abstract: Opioid use disorder (OUD) is a global crisis with high relapse rates, often beginning with prescribed pain medications. Although transcriptomic studies have identified pathways disrupted in OUD, including DNA damage, neuroinflammation, synaptic remodeling, and early neurodegeneration, associated epigenetic mechanisms remain underexplored. We generated multiome datasets from the human postmortem subgenual anterior cingulate cortex (sgACC) and nucleus accumbens (NAc) to investigate cell type-specific epigenetic alterations in OUD. Chromatin state enrichment analysis identified states enriched at transcription start sites (TSS) of differentially expressed genes and ATAC-seq peaks. Single-Cell Regulatory Network Inference and Clustering (SCENIC) was used to define transcription factor (TF) network changes, and active/inactive compartments were examined across cell types. In sgACC, TSS of upregulated genes in VIP interneurons were enriched for constitutive heterochromatin (Het) and bivalent regulatory states (TssBiv), indicating a shift of inactive chromatin toward activation. TSS of downregulated genes in subsets of microglia and astrocytes showed enrichment of proximal promoter regions (TSSFlank), suggesting remodeling of active chromatin. In NAc, TSS of upregulated genes in subsets of dopamine receptor 1+ (D1) cells were enriched for weakly repressed polycomb regions (ReprPCWk), indicating opening of repressive chromatin. TSS of downregulated genes in D1 and D2 neurons showed enrichment for active enhancers (EnhA2), implying reduced enhancer-mediated expression. Differentially accessible peaks in both regions were predominantly enriched in repressive chromatin states, indicating widespread perturbation of repressive regions. TFs associated with transcriptional repression exhibited elevated SCENIC network activity across sgACC cell types, including EP300, MAX, and NR3C1. These results indicate cell type-specific chromatin alterations across brain regions. Overall, the genome appears to loosen, with TF activity facilitating chromatin opening. This may reflect a compensatory response to limit the activation of differentiation programs, thereby explaining increased TF activity that promotes polycomb-associated repression. As cells respond to opioid-related stress, enhanced repression may protect key programs, while other repressed regions become susceptible to disruption, leading to chromatin opening and epigenetic instability.

Disclosures: S.V. Sambare: None. **M. Fish:** None. **V. Cherupally:** None. **B.N. Phan:** None. **C. Srinivasan:** None. **J.R. Glausier:** None. **C. Fu:** None. **D.A. Lewis:** None. **A.R. Pfenning:** None. **M.L. Seney:** None. **R.W. Logan:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.11/JJ18

Topic: H.08. Drugs of Abuse and Addiction

Support: AIMAHEAD

Title: Genomic Feature Engineering for Machine Learning Classification of HIV/SUD Comorbidity

Authors: *R. CHAUHAN[1], M. C. GONDRÉ-LEWIS[2];
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Abstract: HIV and substance use disorder (SUD) are overlapping public health challenges that disproportionately affect underserved communities and may share neurobiological mechanisms involving reward, stress, neurotransmission, and neuroimmune signaling. We developed a genomic feature-engineering workflow using whole-genome sequencing-derived allele count/allele frequency data from 23,575 All of Us participants classified as Control, HIV-only, SUD-only, or HIV+SUD. Quality control reduced 56,993,186 variant sites to 7,179,119 high-quality common biallelic SNPs after PASS, call-rate, and minor allele-frequency filtering. To support biologically interpretable SUD-focused modeling, we created a preliminary literature-guided panel of 25 candidate genes representing dopamine/reward, opioid, stress/HPA-axis, serotonin/mood, glutamate/GABA, and neuroimmune pathways. Verified GRCh38 coordinates were intersected with the All of Us MatrixTable, identifying 5,272 candidate-gene variants across 23,575 participants. Current feature engineering evaluates normalized gene scores, pathway scores, and genome-wide principal components. Gene scores are calculated as mean alternate-allele dosage within each gene to reduce bias from unequal variant counts. Preliminary strict balanced four-class logistic regression models using 120 participants per group showed that pathway scores performed modestly above chance, while PCA20 features produced stronger classification performance. These findings suggest that PCA captures broad genomic structure, whereas candidate-gene and pathway features may provide biological interpretability. Ongoing work will refine candidate-gene selection, evaluate variant-level predictors, apply repeated cross-validation, and integrate genomic features with phenotype, behavioral, and social-determinant data to improve HIV/SUD comorbidity classification.

Disclosures: R. Chauhan: A. Employment/Salary (full or part-time):; Howard University. **M.C. Gondré-Lewis:** A. Employment/Salary (full or part-time):; Howard University.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.12/JJ19

Topic: H.08. Drugs of Abuse and Addiction

Title: Catecholamine dysregulation as a neurobiological framework for illicit stimulant-associated time management deficits in college students

Authors: *Z. COSTANZA[1], L. BEGDACHE[2];
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Abstract: The illicit use of prescription stimulants (e.g., amphetamine salts, methylphenidate) has shown a concerning upward trend among American college students seeking cognitive enhancement. Stimulant medications (e.g., Adderall, Ritalin, Concerta) are primarily used to treat attention deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder predominantly characterized by dopamine (DA) and norepinephrine (NE) imbalance in the prefrontal cortex (PFC). These agents modulate DA and NE neurotransmission primarily by inhibiting monoamine transporter reuptake (e.g., DAT, NET) and reversing vesicular transporter (VMAT2) function through the disruption of the pH gradient, which results in elevated catecholamine signaling in the PFC. In individuals without ADHD, however, catecholamine dysregulation and subsequent supraphysiological DA/NE elevation may impair executive processes mediated by the PFC and overstimulate the brain's reward pathways through an inverted-U dose-response mechanism. We hypothesized that illicit stimulant use would be inversely correlated with time management behaviors that reflect PFC-dependent executive functions (e.g., initiation, planning, organization) among college students. This study employed an anonymous cross-sectional survey via Google Forms and collected 1,410 responses, primarily from college students residing in North America. The study included self-reported data collected using validated scales, including the Substances and Choices Scale (SACS) and the Time Management Scale (TMS). Pearson's correlation coefficients were computed in SPSS v28.0. A negative correlation was found between illicit stimulant usage and timely assignment completion ($r=-0.182$, $p<0.01$), managing schedule to study for exams ($r=-0.077$, $p<0.01$), initiation of long-term assignments at the start of the semester ($r=-0.126$, $p<0.01$), and study-duration estimation ($r=-.069$, $p<0.05$). These findings are consistent with existing models that demonstrate how illicit stimulant use disrupts natural DA/NE signaling and production mechanisms, subsequently impairing prefrontal regulation of crucial time management-related behaviors. This pattern suggests that illicit stimulant use may neurochemically undermine the very cognitive abilities that college students seek to enhance.

Disclosures: Z. Costanza: None. **L. Begdache:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.13/JJ20

Topic: H.08. Drugs of Abuse and Addiction

Title: Geometric Eigenmode-Based Characterization of Cortical Functional Reorganization in Substance Addiction

Authors: *C. FAN[1], A. JULIANO[2], D. PANCHOLI[2], J. C. PANG[3], H. GARAVAN[4];
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Abstract: Introduction: Brain dynamics are fundamentally constrained by cortical geometry. Neural field theory models brain activity as a weighted superposition of geometry-derived cortical eigenmodes. Because substance addiction involves cortical remodeling and widespread functional abnormalities, addiction-related reorganization may disrupt the geometric and hierarchical organization of cortical function. Here, we apply the geometric eigenmode framework to investigate how substance addiction reshapes brain functional organization. **METHODS:** We analyzed ENIGMA-Addiction multi-site resting-state fMRI data from 911 individuals with substance addiction and 544 healthy controls across 21 international sites, including alcohol, cocaine, and nicotine addiction subgroups. Preprocessed BOLD time series were projected onto the fsLR-32k cortical surface and decomposed using the first 225 Laplace-Beltrami geometric eigenmodes derived from the fsLR-32k cortical template following Pang et al. Eigenmodes were grouped by spatial wavelength/frequency, and eigengroup-level modal power, Shannon entropy, Gini coefficient, and L1/L2 norm ratio were calculated to characterize modal power distribution. Imaging measures were harmonized using ComBat, and group comparisons were performed for overall addiction and each subgroup, controlling for age, sex, education, and head motion with Bonferroni correction. **Results:** Individuals with addiction showed functional activity patterns dominated by ultra-long-wavelength modes, with significantly reduced contributions from short-wavelength modes. Consistently, Shannon entropy and L1/L2 ratio were decreased, whereas the Gini coefficient was increased, indicating reduced complexity and greater concentration of modal power. These alterations were bilateral, suggesting whole-brain coordinated rather than localized reorganization. Subgroup analyses revealed highly consistent modal and metric abnormalities in alcohol and cocaine addiction, indicating shared functional alterations across these substances. In contrast, nicotine addiction showed no significant deviations, suggesting potential mechanistic heterogeneity across addictive substances. **Conclusion:** Together, these findings suggest that addiction is associated with functional reorganization marked by enhanced large-scale coordination, weakened local modulation, lower complexity, higher concentration, and coordination-biased spatial dynamics. Different substances may further affect brain function through both shared and substance-specific patterns of alteration.

Disclosures: C. Fan: None. **A. Juliano:** None. **D. Pancholi:** None. **J.C. Pang:** None. **H. Garavan:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.14/JJ21

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R03DA044496
NIH Grant R61DA059906

Title: Temporal aspects of neural responses to reward and punishment in opioid use disorder

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Abstract: The normalization of neural responses to nondrug rewards and punishments is a critical component of recovery from opioid use disorder (OUD). A prior study using fMRI to measure the magnitude of these responses showed no differences between individuals recovering from OUD and healthy controls when using standard analyses that assume a fixed hemodynamic response over time (Bhanji et al., 2025). However, the temporal characteristics of these neural responses to reward and punishment in OUD are not well understood. Here, we applied a time-series random forest classification method to evaluate how the temporal dynamics of brain responses to reward and punishment distinguish individuals going through OUD recovery from healthy control participants.

Twenty-three individuals recovering from prescription OUD (in the first 3 weeks of residential treatment) and 21 healthy, drug-naive control participants completed a card guessing game involving small monetary gains or losses on each trial. fMRI BOLD signal was used to measure event-related brain responses following monetary gains and losses. Event-averaged time series in 12 *a priori* valuation network regions of interest (ROIs) were extracted for a 7.2 s window following gain and loss events in the task (12 time points, TR = 0.6 s). Then, a time-series random forest approach was used to classify participants as OUD or control group based on temporal characteristics of the ROI response over this period following gains or losses. Unlike spatial methods such as multi-voxel pattern analysis, where features are the magnitude of response in each voxel, this approach uses intervals of the response from an ROI (or set of ROIs) to classify between groups. Cross-validated classification accuracy was calculated using repeated random train/test splits. Higher accuracy indicated a greater difference in the ROI response to gain or loss between OUD and control groups.

Gain and loss responses successfully distinguished the groups above chance level in key valuation network regions (e.g., striatum, ventromedial prefrontal cortex). Accuracy was highest (65.91%) when classification was based on left ventral striatum responses to losses. Overall, neural time series following losses were more distinguishable between OUD and control groups than time series following gains. These results suggest that time-series approaches are important for characterizing reward/punishment processing in OUD, offering a promising tool for treatment monitoring and intervention development.

Disclosures: J.P. Bhanji: None. **F. Elsadig:** None. **M.R. Delgado:** None. **S. Ray:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.15/JJ22

Topic: H.08. Drugs of Abuse and Addiction

Support: R41 MD012318 National Institute of Minority Health Disparities (NIMHD/ NIH)
P30AI117970 District of Columbia Center for AIDS Research

Title: Limbic Functional Connectivity in Substance Abusers and People Living with HIV

Authors: *S. D. WASHINGTON[1], A. S. VANMETER[2], M. C. GONDRÉ-LEWIS[3];
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Abstract: Both human immunodeficiency virus (HIV) and substance use disorder (SUD) affect behavioral health and limbic circuitry, including the amygdala, hippocampus, and nucleus accumbens. Neuroimaging studies repeatedly show altered functional connectivity in people living with HIV (PLWH) or SUD. However, previous studies often do not account for HIV/SUD co-morbidities, an oversight that represents a potential confound in studies of both disorders. Here, we obtained resting-state functional magnetic resonance imaging (rsfMRI) data at 3-Tesla from PLWH without a history of SUD (PLWH, N=7), people with SUD but not HIV (SUD-only, N=10), PLWH with SUD (HIV+SUD, N=19), and healthy controls (N=14). Seed-based analyses showed robust hippocampal connectivity with the default mode network (DMN) across all three clinical groups. Connectivity with the DMN was weaker for nucleus accumbens and amygdala seeds. Functional connectivity of the amygdalae in the HIV-only group differed significantly from both controls and the SUD-only group. Specifically, relative to controls, the amygdalae of PLWH showed greater functional connectivity with the medial frontal, as well as the superior frontal, angular, inferior temporal, and middle temporal gyri. Relative to the SUD-only group, the amygdala had greater connectivity with angular and supramarginal gyri, precuneus/intracalcarine and lingual cortices, occipital and middle temporal cortices, and cerebellar Crus II. Relative to the HIV+SUD group, the amygdalae of controls showed greater connectivity with precuneus and supracalcarine cortex, and the hippocampus showed greater connectivity between cuneus, precuneus, and intracalcarine cortex. When compared to the HIV+SUD group, the hippocampi of the SUD-only group had greater connectivity with the precuneus and intracalcarine cortex, but their nucleus accumbens had less connectivity with occipital cortex. Connectivity patterns differed by hemisphere. Although preliminary, these findings suggest that HIV-only, SUD-only, and HIV+SUD groups should be analyzed separately in neuroimaging studies, particularly in populations disproportionately affected by HIV and SUD.

Disclosures: S.D. Washington: None. **A.S. VanMeter:** None. **M.C. Gondré-Lewis:** None.

Poster

PSTR242: Genetic, Translational, and Clinical Studies of Addiction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR242.16/JJ23

Topic: H.08. Drugs of Abuse and Addiction

Title: Neurobehavioral factors associated with vaping cessation in adolescents: implications for health education. A narrative review

Authors: ***J. ARIAS-RICO**[1], E. RAMÍREZ MORENO[2], R. BALTAZAR TELLEZ[5], J. AGUILAR GUTIÉRREZ[3], D. MOLINA AVILEZ[4], O. MARTÍNEZ[6];
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Abstract: The use of electronic cigarettes among adolescents has increased significantly over the last decade, becoming a global public health challenge. Early exposure to nicotine during adolescence can affect neurocognitive processes related to inhibitory control, decision-making, emotional regulation, and brain reward circuits. Although a considerable number of adolescents express a desire to quit vaping, success rates remain limited due to factors such as nicotine dependence, peer pressure, and the use of vaping as a coping mechanism for stress. Recent evidence suggests that certain neurobehavioral factors may either facilitate or hinder cessation. The aim of this work was to analyze the available scientific evidence on neurobehavioral factors associated with vaping cessation in adolescents and discuss its implications for the design of health education strategies aimed at preventing and cessating electronic cigarette use. A narrative review of scientific literature published in biomedical and public health databases was conducted. Observational studies, systematic reviews, meta-analyses, and qualitative research focused on adolescent e-cigarette users were included. Variables related to intention to quit, cessation attempts, risk perception, nicotine dependence, emotional self-regulation, peer influence, and motivation for change were examined. The literature shows that risk perception is one of the main protective factors associated with the intention to quit vaping. Adolescents who recognize the adverse effects of nicotine on health and the brain are more likely to attempt to quit. Likewise, self-efficacy, emotional regulation, intrinsic motivation, and family support are consistently associated with higher cessation rates, vs nicotine dependence, continuous exposure to peers who use e-cigarettes, advertising of vaping products, and the use of vaping as a coping mechanism for anxiety, stress, or emotional problems decrease the likelihood of quitting. Studies report that a significant proportion of adolescents have attempted to quit vaping on multiple occasions but face barriers related to withdrawal symptoms, social pressure, and the availability of electronic devices. The neurobehavioral factors associated with vaping cessation in adolescents involve a complex interplay of cognitive, emotional, and social processes. Risk perception, self-efficacy, emotional regulation, and social support emerge as fundamental elements for promoting cessation. These factors could increase the effectiveness of prevention programs and contribute to protecting brain health during adolescence.

Disclosures: J. Arias-Rico: None. **E. Ramírez Moreno:** None. **R. Baltazar Tellez:** None. **J. Aguilar Gutiérrez:** None. **D. Molina Avilez:** None. **O. Martínez:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.01/JJ24

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R01AA024845

Title: Nucleus Accumbens BDNF-TrkB Signaling Mediates Social and Ethanol Reward

Authors: *C. SCHAEFGEN[1], P. MCKEON[1], A. SICLAIR[1], B. N. MATHUR[2];
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Abstract: The nucleus accumbens (NAc) integrates many inputs to enable cue-reward associations. Alterations in cue-reward association contribute to diseases of addiction, including alcohol use disorder (AUD). How alcohol modulates synaptic plasticity mechanisms governing cue-reward associations is poorly understood. Our lab previously identified a form of inhibitory long-term depression in the NAc (NAc-iLTD) that requires brain derived neurotrophic factor (BDNF) signaling via the tyrosine kinase B (TrkB) receptor. This form of plasticity is enhanced by ethanol in a TrkB-dependent manner. This positions ethanol to disinhibit the NAc and, thereby, enhance reward learning. However, it remains unknown what this TrkB-dependent plasticity in the NAc might be encoding to be co-opted by alcohol. Thus, to examine if a form of natural reward is encoded by NAc TrkB activation, we conducted a social conditioned place preference. In this paradigm, a distinct environmental context is paired with the opportunity to interact with a conspecific to assess the animal's learned preference for environments associated with positive social experiences. We utilized targeted deletion of TrkB upon viral-mediated expression of Cre recombinase in the NAc of mice with loxP sequences flanking the TrkB gene. We found that NAc TrkB is necessary for expression of a social CPP. In addition, we found NAc TrkB knockout significantly diminished social preference in a social three-chamber preference assay. However, we did not observe differences in open field, elevated plus maze, or progressive ratio task performances. Finally, we find that TrkB in the NAc is required for development of a CPP for ethanol. Together these data suggest that ethanol may be hijacking a social reward encoding mechanism in the NAc involving BDNF-TrkB signaling.

Disclosures: C. Schaefgen: None. **P. McKeon:** None. **A. Siclair:** None. **B.N. Mathur:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.02/KK1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH K01 DA055068
Georgia Opioid Abatement Trust

Title: The Effect of Prenatal Cocaine Exposure on Hippocampal Neurogenesis, Fos Ensembles, and Cue-induced Re-exposure of Drug Seeking in the Adult Offspring

Authors: *L. N. CALLAN[1], J. ZEMP[1], A. PATEL[2], S. PATEL[2], U. PATEL[2], F. HOANG[2], L. SANTANA[2], A. GHEIDI[3];
[1]Biomed. Sci., Mercer Univ. Sch. of Med., Macon, GA; [3]Dept. of Biomed. Sci., [2]Mercer Univ., Macon, GA

Abstract: Maternal drug use during pregnancy can disrupt fetal brain development, producing long-lasting changes in neural circuits that may increase susceptibility to substance use disorders later in life. Despite evidence linking prenatal cocaine exposure to behavioral and cognitive deficits, the mechanisms by which it influences relapse vulnerability in adulthood remain poorly understood. This project investigates how prenatal cocaine exposure alters hippocampal neurogenesis, alters vulnerability to future drug seeking, and Fos ensembles. The hypothesis was that prenatal cocaine exposure increases neuronal activity in the hippocampus, as indicated by elevated Fos expression, while reducing hippocampal neurogenesis, as indicated by decreased BrdU labeling, contributing to heightened relapse susceptibility in adult offspring. To investigate this research hypothesis, female Sprague-Dawley rats were paired with male Sprague-Dawley rats and carefully monitored to confirm day of conception or day E0. Dams were then given either two subcutaneous injections of cocaine or saline from days E8-E19 at a dose of 20mg/kg, with saline given at an equivalent dose per weight as control. When offspring were 50-60 days old, they underwent catheter surgery for intravenous self-administration of fentanyl at a dose of 2.5 µl/kg/infusion. After 14 continuous days of training on an FR1 schedule for 3 hours, rats underwent forced abstinence for 14 days in their home cage. During the last 5 days of forced abstinence before re-exposure, rats were given intraperitoneal injections of 5-Bromo-2'-deoxyuridine (BrdU) at a dose of 50 mg/kg. Rats were then placed back in the operant chambers for re-exposure, without the availability of fentanyl. 1.5 hours after the start of re-exposure, rats were transcardially perfused (4% PFA), and brains extracted for triple-stain immunofluorescence for BrdU, NeuN, and c-Fos. Behavioral data showed that both prenatal cocaine-exposed and prenatal saline-exposed offspring were able to distinguish the active lever from the inactive lever during the re-exposure test. However, there was a trend suggesting that saline-exposed offspring showed greater active-lever pressing compared with prenatal cocaine-exposed offspring. These findings did not support our original hypothesis that prenatal cocaine exposure would enhance relapse-like behavior in adulthood. Instead, saline-exposed offspring appeared to show greater motivation during re-exposure. However, additional replications are needed because of the presence of outliers and the need to increase sample size. Immunofluorescence analyses of Fos, BrdU, and NeuN expression are ongoing.

Disclosures: L.N. Callan: A. Employment/Salary (full or part-time):; Mercer University School of Medicine. **J. Zemp:** A. Employment/Salary (full or part-time):; Mercer University School of Medicine. **A. Patel:** None. **S. Patel:** None. **U. Patel:** None. **F. Hoang:** None. **L. Santana:** None. **A. Gheidi:** A. Employment/Salary (full or part-time):; Mercer University School of Medicine.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.03/KK2

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Código de Financiamento 001, bolsa DS (Programa Demanda Social)

Title: Ayahuasca Reduces Sugar Overconsumption in Translational Models of Eating Disorders

Authors: *C. FERREIRA CORONA[1], F. ALVES ALENCAR LIMA[2], P. LUCAS VOGT[3], S. MACHADO ARAUJO BORSTMANN[4], D. MOTER BENVEGNÚ[3], F. PINTO DO NASCIMENTO[5], J. FRANCIESCO VETTORAZZI[5];
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Abstract: The interspecies translational nature of palatable foods reinforcing effects provides a robust framework allowing testing novel therapies for eating disorders. We investigated Ayahuasca psychedelic effects on sucrose intake utilizing *Drosophila melanogaster* and C57BL/6 mice submitted to binge-like eating (BLE) conditions. Initially, we evaluated Ayahuasca's toxicity in *D. melanogaster* exposed to ayahuasca 5, 25, 50, 75 and 100 % (n=300/group). Survival, open-field (n=30-34/group), and negative geotaxis (n=30/group) were assessed at 24 and 48 h. Ayahuasca showed no toxicity at 24h, although survival decreased at 48h for > 25 % concentrations [Log-rank: x^2 (1) = 12.16; p = 0.0005]. The 5 and 50 % concentrations (0.011 and 0.111 mg/mL DMT) enhanced motor performance and reduced climbing time [H (5) = 19.41; p = 0.0016], being used in subsequent trials. Using the Capillary Feeder (CAFE) assay (n=6 replicates/group), we tested these doses in flies with high-sugar diet-induced overconsumption (days 3-4). Sugar-sensitized flies exhibited a significantly higher sucrose (15 %) intake [t(48) = 2.164; p = 0.0357] while ayahuasca completely abolished sugar-induced overconsumption at 5 h [F(3.40) = 3.09; p=0.038], persisting at 24 h [F(3.40) = 4.41; p=0.008; 5 %: p=0.007; 50 %: p=0.024]. Transitioning from invertebrates to a murine model, mice underwent a BLE protocol of 20 h intermittent fasting with restricted access to 17 % sucrose and chow for 10 days. On day 11, only chow was offered, and mice were treated with saline or ayahuasca (1.76 mg/kg DMT; n = 8/group). On day 12, after 48 h of sucrose withdrawal, anxiety-like behavior was assessed in the elevated plus maze. Subsequently, sucrose was reintroduced (52 h of withdrawal) and its consumption was measured. Hypothalamic CART (cocaine- and amphetamine-regulated transcript) gene expression was evaluated 4 days after treatment. Ayahuasca treatment prevented withdrawal-induced hyperphagia in BLE mice, during a 1 h [U = 2; p = 0.0006] but not a 4 h [t(14) = 1.365; p = 0.1938] sucrose re-exposure. Besides, ayahuasca-treated mice showed an improvement in the BLE-induced anxiety-like behavior [F(2.21) = 5.81; p = 0.0098; post hoc p = 0.015]. Mechanistically, 4 days later, whereas the BLE model downregulated hypothalamic CART ayahuasca treatment restored this key anorexigenic neuropeptide levels [F (2.13) = 8.11; p = 0.007; post ho p = 0.026]. Altogether, our translational

data indicates that ayahuasca modulates BLE conserved mechanisms across species, highlighting ayahuasca's therapeutic potential for binge eating disorders.

Disclosures: C. Ferreira Corona: None. **F. Alves Alencar Lima:** None. **P. Lucas Vogt:** None. **S. Machado Araujo Borstmann:** None. **D. Moter Benvegnú:** None. **F. Pinto do Nascimento:** None. **J. Franciesco Vettorazzi:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.04/KK3

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH R00MH135177
BBRF young investigator award

Title: Cocaine-Induced Modulation of Kappa Opioid Receptors in Amygdalostriatal Pathways

Authors: *C. JACOBUS[1,2], L. WOOLDRIDGE[2], J. GIOVANNIELLO[2];
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Abstract: Goal-directed decision making allows behavior to be guided by expected outcomes. Repeated cocaine exposure shifts behavior from flexible, goal-directed actions to inflexible habits. An overreliance on habits can contribute to repetitive and perseverative behaviors characteristic of substance use disorders and other co-morbid neuropsychiatric conditions. However, the neurobiological mechanisms that allow cocaine to promote habits are still unclear. Our previous work has demonstrated that projections from the basolateral amygdala (BLA) to the dorsomedial striatum (DMS) are critical for goal-directed behavior and suppressed when habits form prematurely. Moreover, kappa-opioid receptors, which can engage the endogenous opioid system and inhibit neural activity, are found on BLA-DMS projections. Thus, we asked how kappa-opioid receptors are modulated by repeated cocaine exposure. We hypothesize that cocaine exposure will lead to upregulation of KOR expression in BLA-DMS neurons. To test this hypothesis, a retrograde AAV tracer was injected into the DMS of C57/Bl6 mice to label BLA→DMS neurons. Following cocaine exposure, RNAscope was used to quantify KOR mRNA expression within this pathway. Exploring how cocaine use regulates KOR expression within BLA-DMS projections will provide insight into the neural mechanisms underlying the transition from goal-directed to habitual behavior and lay the foundation for future identification of new treatment approaches for conditions marked by maladaptive habits.

Disclosures: C. Jacobus: None. **L. Wooldridge:** None. **J. Giovanniello:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.05/KK4

Topic: H.02. Reward and Appetitive Learning and Memory

Support: 1K01DA060994-01

Title: Dissociable Effects of Nicotine on Hippocampal-Dependent Reward Learning and Recognition Memory in Mice

Authors: *S. JALIHALKAR, S. KONOW, S. KRISHNAN;
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Abstract: Nicotine acts primarily through nicotinic acetylcholine receptors (nAChRs), which are densely expressed in the hippocampus and support reward-related learning and memory. Because nAChR signaling can modulate hippocampal plasticity depending on the timing and pattern of exposure, nicotine's behavioral effects may diverge with developmental stage. We found that adolescent mice exposed to nicotine for two weeks showed impaired novel object recognition, while nicotine-naïve adults learned a reward-context association more rapidly when nicotine served as the reward. These opposing outcomes motivate a central hypothesis: if developmental nicotine exposure compromises the hippocampal circuitry supporting reward learning, adolescent pre-exposed mice should fail to show the enhanced reward-context learning observed in nicotine-naïve adults.To assess recognition memory, a cohort of adolescent male C57BL/6J mice (PND21-35) received nicotine (oral vapor or subcutaneous injection) or vehicle and were tested on a novel object recognition (NOR) task. Nicotine-treated mice showed a lower discrimination ratio than vehicle controls, indicating impaired recognition memory following adolescent nicotine exposure. To investigate nicotine-reward learning, adult male C57BL/6J mice (PND90-100) were head-fixed, water-restricted, and trained on a virtual reality (VR) linear track, where they received oral nicotine or water rewards via a lick spout after completing each 2-m lap. The number of rewards earned and licking behavior were recorded to assess learning. Nicotine-rewarded mice ran significantly more laps per day than water controls, earning more rewards and indicating that nicotine drives stronger reward learning. To confirm both systemic exposure and central nervous system penetration, blood and brain tissue were collected immediately after the final training session for quantification of nicotine and its primary metabolite cotinine by mass spectrometry.Together, these findings reveal differential effects of nicotine on memory and reward learning, suggesting that nicotine strengthens reward-context associations in adult VR learning while impairing recognition memory following adolescent exposure. Next, to directly test whether developmental exposure alters reward learning, we will train adolescent nicotine-pre-exposed mice on the head-fixed VR paradigm in adulthood and compare their acquisition to that of nicotine-naïve controls. In parallel, two-photon calcium imaging of CA1 during VR navigation will define the circuit-level mechanisms underlying these effects across development.

Disclosures: S. Jalihalkar: None. **S. Konow:** None. **S. Krishnan:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.06/KK5

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Start-Up Funds, Temple University

Title: Neurite density along heterogenous mesolimbic circuits is associated with substance use severity

Authors: *R. MOPURU[1], J. K. LEONG[4], N. D. VOLKOW[5], V. P. MURTY[6], I. R. OLSON[2], B. L. ELLIOTT[3];
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Abstract: Background: Mesolimbic dopamine circuits play a central role in drug reward, conditioning and salience attribution and are implicated in the vulnerability for substance use and addiction. Prior preclinical and clinical work has documented functional abnormalities within these networks; and recently a study showed that repeated drug administration triggered myelination of the mesolimbic dopamine circuit in the ventral tegmental area (VTA), which modulated drug seeking behavior in mice (Yalçın et al., 2024). However, little is known whether microstructural changes in white matter are associated with substance use in humans as a function of severity. **Methods:** Participants were drawn from the Human Connectome Project (HCP) 7T diffusion MRI cohort. Substance use was indexed using a latent factor score derived from the broader HCP 1200 release that captures severity across multiple substance classes (Loganathan & Tiego, 2023). Probabilistic tractography was used to reconstruct VTA projections to the hippocampus, nucleus accumbens (NAc), and amygdala. Neurite density index (NDI) was estimated using neurite orientation dispersion and density imaging (NODDI). Tracts were divided into 100 nodes, and NDI was sampled at each node. Cluster-based permutation testing identified consecutive tract segments associated with substance use severity _while controlling for sex, handedness, intracranial volume, head motion, streamline count, and mean streamline length. **Results:** Higher substance use severity was associated with elevated NDI in the left VTA-hippocampus tract (nodes 16-39; b=4.83, p<.001), left inferior VTA-NAc tract (nodes 44-75; b=2.19, p=.006), and left VTA-amygdala tract (nodes 28-99; b=8.25, p<.001). No significant associations were observed in the superior VTA-NAc tract. Right hemisphere clusters were present but did not survive permutation correction. Perceived stress, measured using the percieved stress scale, selectively moderated the VTA-amygdala association, such that the relationship between NDI and substance use severity was stronger among individuals reporting higher stress (b=-0.31, SE=0.16, p=0.047). **Conclusions:** Substance use severity was associated with increases in neurite density across multiple mesolimbic VTA pathways involved with reward, emotional salience and conditioned memory, with stress-related processes appearing particularly relevant to VTA-amygdala connectivity. Further work is required to determine if increases in neurite growth reflect increased myelination and/or pathological connectivity.

Disclosures: R. Mopuru: None. **J.K. Leong:** None. **N.D. Volkow:** None. **V.P. Murty:** None. **I.R. Olson:** None. **B.L. Elliott:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.07/KK6

Topic: H.02. Reward and Appetitive Learning and Memory

Support: 1K01DA060994-01

Title: Development of an Ethanol-Rewarded Head-Fixed Paradigm in Mice for Hippocampal Place Cell Imaging

Authors: *A. MSALEK[1], M. KAKANI[1], S. KRISHNAN[2];
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Abstract: Alcohol use disorder impacts millions of adults in the US annually. Environmental contexts associated with alcohol have shown to evoke cravings and drug-seeking behaviors. Hippocampal place cells, a cellular substrate for contextual memories, may be involved in formation of ethanol-context associations. Two-photon (2p) calcium imaging combined with a virtual reality (VR)-based behavioral paradigm offers a powerful approach to study place cell activity during ethanol-seeking; however, standard head-fixed VR training protocols rely on water restriction to motivate mice to navigate VR environments for liquid rewards. Because water restriction may confound ethanol consumption, metabolism, and reward-seeking behavior, the goal of the project was to establish a water-deprivation-free, ethanol-rewarded, head-fixed spatial learning paradigm suitable for 2p imaging of the hippocampus. First, we sought to find out whether pre-exposure to ethanol may be motivational signal enough for animals to train for ethanol rewards. Two non-water-deprived, ethanol-rewarded cohorts of adult male C57BL/6J mice were established. The first served as a pre-exposure cohort, recieving ethanol per a Drinking-in-the-Dark (DID) paradigm, reaching a maximum ethanol consumption of 4.5 g/kg over 3 hours. The second served as an ethanol naive cohort, receiving the same DID protocol with a water bottle rather than ethanol. A third cohort of water-restricted mice served as a baseline control group. Cohorts were trained on a 2m VR linear track task in which completion of each trial triggered delivery of a 4 μL liquid reward via a lick spout. Anticipatory licking, defined as licking concentrated during the final third of the trial (60cm before the reward) and the licking to dispensed reward during the inter-trial interval, served as the primary behavioral readout of task learning. Both pre-exposed and ethanol naive cohorts received 15% ethanol as a reward, while the baseline control group received water. Ethanol-rewarded mice without water deprivation failed to exhibit organized anticipatory licking, instead distributing licks across the entirety of each lap rather than concentrating them near the reward zone, compared with the water-restricted baseline controls. No consistent differences in licking behavior or task acquisition were observed between the ethanol pre-exposed and ethanol-naive groups, suggesting

that prior ethanol exposure alone does not provide sufficient motivational value under these task conditions. Ongoing projects are exploring sucrose-fading and modified water restriction protocols as alternative strategies for ethanol-rewarded VR task learning.

Disclosures: A. Msalek: None. **M. Kakani:** None. **S. Krishnan:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.08/KK7

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH R21DA058205
McNair Scholars Program
Semmes Summer Undergraduate Research Fellowship
Dr. Harold Murray Research Fund
Departments of Biology and Psychology funds

Title: Oxytocin as potential treatment for cocaine addiction: examination of dopamine firing strength and oxytocin-dependent mechanisms in the VTA

Authors: E. STRATTON[1], D. NUTTER[1], F. GAMBACORTA[1], Y. DURON[1], A. ALLEN[1], C. VILLARREAL[2], G. LE[1], J. STALL[1], K. WOLFHOPE[1], K.-C. LEONG[3], *G. M. BEAUDOIN, III[4];
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Abstract: Cocaine addiction's main mechanism lies in the overactivation of the brain's central reward pathway, which primarily involves an increase in dopamine activity. When significantly overexpressed in this pathway, increased dopamine leads to compulsive drug-seeking behaviors and other lasting implications of addiction, many of which involve the ventral tegmental area (VTA), which is a brain region containing dopaminergic neurons necessary for encoding reward. Oxytocin has been associated with targeting this reward system and potentially reducing drug seeking behavior, therefore it is necessary to study the effect of oxytocin on dopamine cell firing. To investigate this relationship in a rodent model, we examine the effects of bath administration of oxytocin on the spontaneous firing rates of dopamine neurons, and in separate experiments, the frequency and amplitude of miniature excitatory and inhibitory postsynaptic currents in the VTA. Utilizing electrophysiology and a current clamp protocol for recording membrane potential changes, we observe the effects of washing in oxytocin on oxytocin receptor-mediated signaling in the cell, which causes the cell to fire at a different rate. We hypothesize this is mediated by direct activation of Oxytocin receptor (OxtR) expression in dopamine neurons.
To induce loss of expression of OxtR, we are using viral-mediated expression of shRNA to OxtR either globally or only in Dopamine neurons, using transgenic DAT-cre rats. Our immunostaining demonstrates significant loss of expression in cells marked with GFP.

Expression of shRNA globally in the VTA led to loss of an effect on cell firing in dopamine neurons. We are testing if loss of OxtR confined to DA neurons leads to the same effect. This leads us to better understand oxytocin-dependent mechanisms on a molecular level.
The combined utilization of electrophysiology, immunostaining, and confocal microscopy demonstrates the complex relationship between oxytocin and DA activity. This study, as part of a larger project examining the mechanisms of oxytocin on a rodent model, also done in collaboration with behavioral data from Dr. Leong's Laboratory, focuses on how oxytocin can potentially block preference for cocaine, and contributes to data exploring oxytocin as a treatment option for cocaine addiction.

Disclosures: E. Stratton: None. **D. Nutter:** None. **F. Gambacorta:** None. **Y. Duron:** None. **A. Allen:** None. **C. Villarreal:** None. **G. Le:** None. **J. Stall:** None. **K. Wolfhope:** None. **K. Leong:** None. **G.M. Beaudoin:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.09/KK8

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R00MH135177
T32DA007237
BBRF Young Investigator Award

Title: Exploring striatal opioid signaling as a driver of cocaine-potentiated habit

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Abstract: Animals balance flexible, goal-directed strategies and inflexible, habit-driven strategies to make decisions. Interestingly, repeated exposure to psychostimulant drugs like cocaine can promote habit-driven behavior. The mechanisms by which psychostimulants impact the nervous system to bias behavior toward habits remain poorly understood. Cocaine also disrupts the expression of endogenous opioid peptides, such as dynorphin, within striatal regions that drive action selection, but the behavioral impact of this disruption is not well-characterized. Here, we investigate the hypothesis that cocaine exposure promotes habit formation by interfering with dynorphin neurotransmission in the dorsomedial striatum (DMS), itself a crucial driver of goal-directed behavior. Adult male and female C57bl/6j mice were treated with cocaine (30 mg/kg, i.p.) or saline for 6 days. Following a week of abstinence, mice underwent limited action-outcome training, then were subjected to outcome-specific devaluation probes, a gold-

standard procedure to assess goal-directed vs. habitual behavior. Saline-treated mice reduced lever pressing after outcome devaluation compared to a non-devalued control condition, indicating a goal-directed behavioral strategy. In contrast, cocaine-treated mice exhibited similar behavior under both conditions, reflecting insensitivity to outcome devaluation indicative of habit-driven behavior. Behavioral effects were present in both male and female mice. Then, to understand how cocaine alters DMS dynorphin neurotransmission during learning and habit formation, we expressed the dynorphin sensor kLight1.3 in the DMS of saline- and cocaine-treated mice. Using fiber photometry, we then recorded moment-to-moment dynorphin dynamics during cocaine exposure, action-outcome training, and outcome-specific devaluation. Expected results will provide a novel mechanism for cocaine-potentiated habits. This will expand our basic understanding of habit-driven behavioral control as well as contribute translationally relevant insights into the mechanisms by which drugs of abuse impact motivated behavior.

Disclosures: L.M. Wooldridge: None. **C. Jacobus:** None. **E. Townsend:** None. **M.G. Kutlu:** None. **J. Giovanniello:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.10/KK9

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Georgia Opioid Abatement Trust Grant GR00785
NIH K01 DA055068

Title: mPFC Alpha-Adrenergic Receptor Antagonism During Fentanyl and Sugar Context-Induced Re-exposure

Authors: *J. ZEMP[1], L. CALLAN[2], A. CAROLAND-WILLIAMS[2], U. PATEL[3], F. HOANG[3], D. PATEL[1], A. PATEL[3], C. ARANT[3], C. ARANT[3], J. C. GAINES[2], R. RUDD[2], A. GHEIDI[2]; [2]Biomed. Sci., [1]Mercer Univ. Sch. of Med., Macon, GA; [3]Col. of Liberal Arts, Mercer Univ., Macon, GA

Abstract: Background: Re-exposure to contexts where rewarding experiences occurred is capable of recapitulating seeking and taking behavior in rodents. Cue-induced reward-seeking is known to involve noradrenergic signaling within the medial prefrontal cortex (mPFC), but the effects of α1-adrenergic receptors on context-induced reward-seeking remain unclear. We hypothesized that α1-adrenergic receptor antagonism within the mPFC would reduce context-induced re-exposure of sugar-seeking and fentanyl-seeking. Methods: Adult male and female Sprague Dawley rats were trained on a fixed ratio 1 schedule for 10 days to associate active lever pressing with the delivery of sugar pellets (1 h/day) or intravenous fentanyl infusions (2.5 μg/kg/infusion; 3 h/day) on an FR1 schedule. After 2-weeks of abstinence in the home cage, rats received bilateral intra-mPFC microinjections of either the α-adrenergic receptor antagonist

Terazosin (3μg in 0.5μL aCSF/ hemisphere) or vehicle control before immediately being placed back into the training context for a 1-h re-exposure test without cue light or rewards available. Results: During acquisition, both male and female rats learned to discriminate between the active and inactive levers, preferentially pressing the active lever for sugar pellet and fentanyl delivery. For sugar acquisition, males lever pressed more than females but did not earn more rewards due to persistent pressing during the time-out period. For fentanyl acquisition, no sex-dependent analyses were conducted due to a small sample size. Upon context-induced re-exposure, rats continued to press the active lever despite the absence of reward and associated cue. Notably, analysis of the initial 15 minutes of re-exposure revealed that mPFC Terazosin infusions significantly increased active lever pressing for sugar rewards compared to vehicle controls. Fentanyl analysis is pending. Conclusion: While studies investigating the effects of Terazosin on fentanyl-seeking are ongoing, these findings demonstrate that the α1-adrenergic receptor antagonist Terazosin unexpectedly potentiates the retrieval of natural reward memories. In this context, blocking α1-adrenergic receptors in the mPFC may enhance the brain's tendency to update information, such as where task performance relies on recalling a familiar learning environment with some changes (no discrete cues).

Disclosures: J. Zemp: A. Employment/Salary (full or part-time):; Mercer University School of Medicine. **L. Callan:** None. **A. Caroland-Williams:** None. **U. Patel:** None. **F. Hoang:** None. **D. Patel:** None. **A. Patel:** None. **C. Arant:** None. **C. Arant:** None. **J.C. Gaines:** None. **R. Rudd:** None. **A. Gheidi:** A. Employment/Salary (full or part-time):; Mercer University School of Medicine.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.11/KK10

Topic: H.02. Reward and Appetitive Learning and Memory

Support: K01AA027832

Title: Characterizing probabilistic stimulus-response learning for alcohol in risky social drinkers

Authors: *T. T. HAN[1], J. G. PRATT[2,3], S. KANG[2], K. B. LOETSCHER[2], E. V. GOLDFARB[2]; [1]Psychiatry, [2]Yale Univ., New Haven, CT; [3]UCLA, Los Angeles, CA

Abstract: Chronic alcohol and substance use potentiate habit formation in preclinical models, reflecting a shift from goal-directed behavior toward habitual stimulus-response (S-R) associations, with activity migrating from prefrontal cortical to striatal premotor circuits. Whether S-R associations play a role in recreational human substance use—and whether they reflect a general learning change or one specific to the favored substance—remains unclear. Because binge/heavy recreational use marks a window of vulnerability to addiction, characterizing learning during this period is informative. We used a reinforcement-learning task

with reversal and devaluation phases to assess S-R associations and striatal circuitry in human social drinkers.
Participants played a game in which they learned probabilistic associations between stimuli (object image) and responses (door selection, 80% reinforced), each of which was reinforced with a stimulus-specific outcome (fruit image). On interleaved trials, they learned about alcohol and non-alcohol object stimuli, enabling tests of alcohol-specific learning biases. We recruited light drinkers (no binges, n=40, mean age=25.0, SD=5.9) and regular binge/risky drinkers (n=37, age=24.4 [5.8]). Trial-by-trial choices were fitted by a reinforcement-learning model, and functional connectivity was computed for goal-directed (mPFC-caudate) and habit (premotor-putamen) circuits. Risky drinkers showed stronger, substance-specific acquisition of alcohol associations (p=.028). They also showed greater spreading of alcohol-related value, preferring fruit outcomes that had been paired with alcohol stimuli (group×cue p=.003; alc-tool p<.0001). During reversal and devaluation, light drinkers updated alcohol cues more than neutral cues, whereas risky drinkers showed no differential updating and more perseverative responding to alcohol (p=.020), indicating more rigid alcohol associations. Preliminary neuroimaging results indicate overall higher background corticostriatal connectivity in light drinkers. Notably, a higher alcohol learning rate was associated with weaker mPFC-caudate coupling (p=.04). This effect was specific to the alcohol learning rate, robust to AUDIT severity, and strongest with connectivity during early learning.
These findings provide evidence that risky drinking is associated with enhanced, alcohol-specific acquisition and impaired updating of alcohol S-R associations, accompanied by reduced goal-directed corticostriatal coupling. Ongoing analyses examine how striatal circuitry supports rigid alcohol-related associations.

Disclosures: T.T. Han: None. **J.G. Pratt:** None. **S. Kang:** None. **K.B. Loetscher:** None. **E.V. Goldfarb:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.12/KK11

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Takeda Science Foundation
Uehara Memorial Foundation
AMED JP24gm6910012
JP24wm0625210
JSPS KAKENHI JP26H01169
JP21K07259
JP25K02377
JP24H02163
JP21K19428
JP21H05169

JP22H04998
JP22KJ1760
JP21J40030

Title: Cell-type-targeted fiber photometry reveals motivational outcome discrimination by μ-opioid receptor-expressing populations in a macaque

Authors: *S. AMEMORI[1], K. KUBOTA[2], M. NAGATSUKA[2], K.-I. AMEMORI[1];
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Abstract: The μ-opioid receptor (MOR) system is commonly associated with reward processing, but it is also implicated in aversive responses. Whether MOR-expressing neuronal populations selectively signal reward or also discriminate non-rewarding and aversive outcomes remains unclear, especially in nonhuman primates, where cell-type-targeted activity measurements are technically challenging. To address this question, we expressed GCaMP6f under the control of the mMORp promoter and used fiber photometry to record activity from MOR-expressing populations in the amygdala and head of the caudate nucleus of a female Japanese macaque during a Pavlovian cue-outcome task. Each trial began with 1 s of central fixation, followed by presentation of one of three visual cues for 1 to 1.5 s. The cues predicted reward, no reward, or air-puff outcomes, and the predicted outcome was delivered after successful fixation. Behavioral performance indicated that the macaque used the cues to anticipate upcoming outcomes: fixation-break rates differed significantly across cue conditions (repeated-measures ANOVA, $F(2,22) = 97.85$, $p < 0.001$), with the highest break rates for air-puff-predicting cues. To quantify cue-related and outcome-related activity, calcium signals were analyzed during predefined time windows. Cue-related activity was measured 0.5 to 1.0 s after cue onset, and outcome-related activity was measured 1.5 to 2.5 s after outcome delivery. For each recording site, significant differences among reward, no-reward, and air-puff conditions were identified using one-way ANOVA ($p < 0.05$). Outcome-related discrimination was more common than cue-related discrimination. In the amygdala, 2 of 28 sites discriminated cues and 6 of 28 discriminated outcomes; in the head of the caudate nucleus, 0 of 14 sites discriminated cues and 3 of 14 discriminated outcomes (exact McNemar test across all sites, $p = 0.016$). Response profiles were heterogeneous, indicating that MOR-expressing populations did not simply show a uniform reward-related response. Together, these findings demonstrate that cell-type-targeted fiber photometry can reveal activity patterns of MOR-expressing populations in macaque limbic and striatal circuits during behavior. MOR-expressing populations discriminated experienced outcomes across reward, no-reward, and air-puff conditions, with outcome-related discrimination being more prominent than cue-related discrimination. These results suggest that primate MOR-expressing circuits participate in processing not only reward, but also non-rewarding and aversive outcomes.

Disclosures: S. Amemori: None. **K. Kubota:** None. **M. Nagatsuka:** None. **K. Amemori:** None.

Poster

PSTR243: Drugs, Addiction, and the Remodeling of Reward

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR243.13/KK12

Topic: H.02. Reward and Appetitive Learning and Memory

Support: DA045913
P50DA046346
R01AA028215

Title: Determining mechanistic differences in multiple drug- and fear-associated memories

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Abstract: Substance use disorder (SUD) and post-traumatic stress disorder (PTSD) are often comorbid, long-lasting, and resistant to treatment. Cues associated with drug use or traumatic events become consolidated into strong memories. When these cues are encountered, they can lead to recall of the associated memories, resulting in resumption of substance use or presentation of anxiety- or fear-like behaviors. Drug- and fear-associated memories are often examined singly, but not frequently together in the same animal. Here, we aimed to examine the interplay between them. Based on pilot data, we first explored whether fear conditioning took place relative to cocaine self-administration acquisition and if this would affect cue-induced reinstatement. Rats underwent fear conditioning before or after cocaine or sucrose self-administration, then underwent instrumental extinction followed by cue-induced reinstatement. Groups that underwent no fear conditioning were also included. Interestingly, rats that underwent fear conditioning after acquisition, but not before, had attenuated cue-induced reinstatement. This suggests that the timing of fear conditioning can affect subsequent cocaine seeking after extinction. To explore this further, we next examined cellular activity following recall of a single or both fear- and cocaine-associated memories. We included groups that underwent cocaine or saline self-administration, with fear conditioning occurring before or after acquisition, as well as a naive group. Rats then underwent a recall session (fear-, cocaine-, or both-associated memories) before brains were processed for cFos expression. In several brain regions (e.g., infralimbic medial prefrontal cortex, nucleus accumbens, dorsal hippocampus), there was decreased cFos density in groups that underwent fear conditioning after cocaine self-administration, regardless of which memory was recalled. Overall, the results indicate that the order of fear conditioning and cocaine self-administration can affect later cue-induced reinstatement and change neural activity levels in several learning- and SUD-related brain regions. Unfortunately, examining the mechanisms underlying both cocaine- and fear-associated memories, and how they might interact, is not well explored. Determining unique or overlapping mechanisms could lead to novel therapeutic options.

Disclosures: M. Hafenbreidel: None. **R.H. Cole:** None. **A. Obeng:** None. **C. Forbes:** None. **M.M. Torregrossa:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.01/KK13

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 2R01 DA029718
NIH Grant RF1DA048808
NIH Grant R21DA042597

Title: Development and Validation of a Vaporizing Model for Noninvasive Self-administration of Cocaine in Mice

Authors: *Q. WANG[1], Y. LIU[1], G. F. KOOB[2], L. F. VENDRUSCOLO[2], N. D. VOLKOW[3], C. DU[1], Y. PAN[1];
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Abstract: Development and Validation of a Vaporizing Model for Noninvasive Self-administration of Cocaine in Mice
Qiaochu Wang[1†], Yanzuo Liu[1†], George F. Koob[2], Leandro F. Vendruscolo[2,3], Nora D. Volkow[3], Congwu Du[1], and Yingtian Pan[1]
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[†]: **Q.Wang and Y.Liu:** contributed equally
Competing Interests: No competing interests
AbstractIntravenous self-administration is widely considered as the gold-standard paradigm for studying the neurobiological mechanisms underlying drug addiction in rodents. However, its application in mice is often limited by technical challenges associated with chronic intravenous catheterization, including catheter blockage or occlusion. To overcome these limitations, we developed and validated a noninvasive vapor-based cocaine self-administration model in mice. In this study, mice were trained to self-administer vaporized cocaine under fixed-ratio reinforcement schedules, FR1 and FR3, and were tested under both short-access (ShA, 1h/day) and long-access (LgA, 3h/day) conditions. Our results show that vaporized cocaine induced increased locomotor activity in mice. Also, mice showed robust self-administration of vaporized cocaine and increased operant responding under higher reinforcement requirements. In addition, exposure to extended daily access to cocaine vapor via self-administration led to escalation of cocaine vapor intake, emulating compulsive-like drug use observed in humans. These findings are consistent with the behavioral and physiological features related to cocaine use disorder, supporting vaporized cocaine self-administration as a viable mouse model for preclinical addiction research. By circumventing the need for intravenous catheterization, this approach reduces surgical burden and animal stress, supports longitudinal experimental designs, and is

compatible with various neurogenetic and imaging techniques, including optogenetics and brain imaging in freely moving mice.
AcknowledgementsThis work was supported in part by National Institutes of Health (NIH) grants 2R01 DA029718 (C.D., Y.P.), RF1DA048808 (Y.P., C.D.), R21DA042597 (Y.P., C.D.) and NIH's Intramural Program of NIDA (G.K., L.F.V.) and of NIAAA (N.V.).

Disclosures: Q. Wang: None. **Y. Liu:** None. **G.F. Koob:** None. **L.F. Vendruscolo:** None. **N.D. Volkow:** None. **C. Du:** None. **Y. Pan:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.02/KK14

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIA R25AG076396 (BB, CR)
Alzheimer's Association Research Grant AARGD-22-972117 (AMP)
R25AG086095

Title: Tracking of cocaine-related behaviors in a novel model of controlled oral administration

Authors: *I. NIEVES[1], A. CALAVIA[2], A. MARTIN-PEÑA[2];
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Abstract: Psychomotor sensitization is a phenomenon characterized by progressive increases in locomotor activity following repeated, intermittent exposure to cocaine. It is a form of behavioral plasticity thought to underlie certain aspects of addiction. Locomotor activity is a quantifiable metric widely used to assess cocaine-induced behavioral plasticity in rodents. However, locomotor responses following controlled oral cocaine exposure have yet to be well characterized in Drosophila melanogaster. We have developed a novel feeding protocol that enables quantitative analysis of psychomotor activity in D. melanogaster following intermittent oral cocaine administration, establishing a preliminary behavioral model that we will use to investigate the functional circuits underlying cocaine-induced neural plasticity. Our novel feeding protocol involves immobilizing individual flies at the end of a pipette tip, with the tip subsequently trimmed to expose only the head. To ensure control over the feeding process, eight to ten flies were individually administered either cocaine dissolved in sucrose or sucrose alone, which was administered directly from a micropipette after a 16 to 18-hour starvation period to encourage consumption. Following administration of either cocaine or sucrose, individual flies were placed in an open arena and recorded for 60 minutes to capture locomotor activity. These videos were analyzed using a custom-made tracking software developed to extract locomotor components such as speed and distance traveled. Preliminary analyses suggest that high doses of cocaine above 100 nanograms induced sedation, while moderately high doses induced hypoactivity. In contrast, control flies exhibited relatively higher walking speeds than cocaine

fed flies. Our preliminary data indicates a period of hypoactivity in D. melanogaster that occurs after oral administration of cocaine at relatively high doses of 100 ng and below. While psychomotor responses to volatilized cocaine have been characterized and reported in literature, much less is known about the locomotor effects following controlled oral administration in D. melanogaster. Our feeding paradigm, along with the automated tracking method described here, provides a novel framework for studying dose-dependent behavioral effects of oral cocaine consumption and the neural mechanisms underlying cocaine-induced psychomotor sensitization.

Disclosures: I. Nieves: None. **A. Calavia:** None. **A. Martin-Peña:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.03/KK15

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Research Training Grant T32GM142521-05
NIMH Grant R01-MH111604
NIDA Grant R01-DA040621
NIDA Grant R01-DA066149

Title: Characterization of Sex Differences in the Mouse Cocaine Self-Administration Model

Authors: *A. J. MCQUENEY[1], D. ANDERSON[1], A. ROBISON[2];
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Abstract: Cocaine use disorder remains a significant healthcare crisis with no FDA-approved pharmacological treatments currently available. Additionally, pronounced differences in the ways males and females respond to cocaine have been observed both clinically and in preclinical rodent models. It is therefore imperative that we further investigate the mechanisms of sex differences in cocaine use disorder (CUD) and identify pharmacological targets underlying these differences. Intravenous self-administration (IVSA) measures volitional intake of a drug and is the gold standard preclinical CUD model, allowing investigation of motivation, escalation, and relapse to drug use. Although sex differences in cocaine self-administration have been examined in rats, there is currently a lack of studies characterizing this difference in mice. This is a critical gap because mice are more genetically tractable for manipulation of the receptors and circuits driving the development of CUD and offer a higher throughput and reduced cost compared to other rodents. To establish sex differences in the mouse cocaine IVSA model, male and female mice were surgically implanted with an indwelling jugular catheter and trained in operant boxes to respond for intravenous infusions of cocaine in daily two-hour sessions for 14 days. At a dose of 0.5 mg/kg/infusion, female mice earned more cocaine infusions during the acquisition and stabilization stages and consumed more cocaine across the two-week period. This suggests that female mice are more sensitive to this dose of cocaine, mirroring findings in rat models as well

as humans. Ongoing work characterizes the responses of male and female mice to higher and lower doses of cocaine. Additionally, the effects of gonadectomy in male and female mice are being examined to uncover any role for endogenous sex hormones in cocaine pharmacodynamics. The results of these findings will build the foundation for future genetic and hormonal manipulations to better understand differences in male and female seeking and taking of cocaine. This may help inform the development of precision treatments for CUD that consider both biological sex and hormonal state.

Disclosures: A.J. McQueney: None. **D. Anderson:** None. **A. Robison:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.04/KK16

Topic: H.08. Drugs of Abuse and Addiction

Title: Sex differences in cocaine-induced anxiety and social buffering of cocaine-conditioned avoidance

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Abstract: A growing body of research shows that social interactions influence motivation for drugs of abuse. Despite this, investigations into how social interactions shape neurobiological responses to drugs that may drive motivation are few. Our laboratory uses a cocaine place conditioning model to assess cocaine induced reward and aversion. Human and animal studies demonstrate that cocaine (COC) administration produces initial reward which then gives way to dysphoria. Indeed, rats develop a conditioned place preference (CPP) to the immediate effects of COC (0-5 min after administration) and a conditioned place aversion (CPA) to the delayed effects of COC (15 min after). It is likely that the rewarding and aversive effects of COC contribute to drug taking via positive and negative reinforcement mechanisms, respectively. To assess how social interaction affects COC conditioned reward and aversion we used a procedure in which rats learn to associate a unique environment with either the immediate or delayed effects of one of three doses of COC (0.1mg/kg, 0.25mg/kg, and 1.0mg/kg, IV). Further, during each conditioning session, rats were either alone in the environment (as is typical in these procedures) or they were paired with a same-sex cage mate that never received drug. All animals underwent a post-conditioning test. We replicated previous studies showing that 1.0mg/kg COC produces robust CPP and CPA in male rats, and extended current knowledge to show that while female rats developed COC CPP similar to male rats, there was greater heterogeneity in CPA expression in female rats. Using vaginal cytology we tracked estrus cycle phases during place conditioning to show that expression of cocaine conditioned aversion is cycle-dependent. Further, while 1.0mg/kg COC produced a CPA in males conditioned alone, male rats conditioned

with a conspecific failed to develop a CPA, evidencing social buffering of cocaine aversion. Male conspecifics failed to develop a CPP or a CPA. Interestingly, some female rats did exhibit a CPA for environments paired with the delayed negative effects of cocaine, and so did their conspecifics, suggesting a social transfer of cocaine-induced aversion. These data highlight sex differences in cocaine conditioned aversions and suggest that cocaine-induced aversion may be socially transferred to a familiar conspecific in female rats.

Disclosures: L. Moyer: None. **A. Colburn:** None. **M. Kanzaki:** None. **N. Blanco:** None. **I. Jarosek:** None. **V. Mai:** None. **J.M. Wenzel:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.05/KK17

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA055299
NIDA Grant DA050243
NIDA Grant DA055553
NIDA Grant DA044223

Title: A replication study of cocaine reinforcement in spontaneously hypertensive rat substrains: Expansion to ultrasonic vocalizations, transcriptomics, parental origin effects in reciprocal F1 crosses, and fentanyl locomotion

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Abstract: Stimulant use disorders resurged, with increased overdose deaths. Despite high heritability, few genome-wide significant associations have been identified. Genetic mapping of addiction-relevant traits in near-isogenic rodent substrains can facilitate causal gene identification. We previously reported enhanced cocaine intravenous self-administration (IVSA), impulsivity, and compulsivity in SHR/NCrl vs. SHR/NHsd substrains purchased from different vendors. Here we sought to test for replication of cocaine IVSA differences by breeding substrains in-house to control the environment. Furthermore, we expanded to phenotyping cocaine-linked ultrasonic vocalizations (USVs), fentanyl locomotor sensitivity, and transcriptome analysis via bulk RNA-seq of naïve tissue from frontal cortex and striatum of SHR substrains and reciprocal F1 crosses. Adult substrains were tested for acquisition of cocaine IVSA, motivation to acquire cocaine under multiple reinforcement schedules, and dose-dependent rates of responding followed by extinction training and cue-induced reinstatement.

SHR/NCrl rats consistently earned more infusions across schedules, replicating the SHR/NCrl pro-addiction phenotype. Both substrains showed similar extinction rates but SHR/NCrl showed greater reinstatement of lever pressing and USVs following drug-paired cues. SHR/NCrl also showed greater fentanyl locomotor sensitivity vs. SHR/NHsd. In just one vignette from the -omics analysis, SHR/NCrl showed striatal downregulation of astrocyte and microglial activation (C1qa, C1qb, C1qc, Trem2, Fcgr2b, Ingr1, Ager, Cntf), predicting synaptic remodeling/wiring, an upregulation of multiple HSPs and chaperone proteins involved in proteostasis/ER_stress/unfolded protein response, and an upregulation of TLR3->TRIF innate immune signaling (previously associated with increased cocaine reward/plasticity. To summarize, we have replicated and expanded pro-addiction phenotypes across behaviors, biological enrichment terms, and drug classes in SHR/Crl rats.

Disclosures: B.M. Baskin: None. **E.J. Sandago:** None. **E.P. Duffy:** None. **H. Chen:** None. **K.M. Kantak:** None. **C.D. Bryant:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.06/KK18

Topic: H.08. Drugs of Abuse and Addiction

Support: NIMH129320
NIDA051598
NIDA051977

Title: Behavioral flexibility and persistence following transitions between long and intermittent access to drug and non-drug reward

Authors: *K. M. WILLIFORD[1], I. D. DALY[1], A. SHIN[2], E. GUAN[2], S. KIM[2], H. LOVE[2], S. MAGNUS[2], H. ROLLS[2], A. SERRATOS[2], S. M. GROMAN[3];
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Abstract: Schedules of drug availability critically influence the development of addiction-like behaviors. For example, extended ("long") access, but not short access, cocaine self-administration reliably produces escalation of intake and the emergence of compulsive drug seeking in a subset of animals. More recently, intermittent access procedures, which better model fluctuating drug levels observed in human substance use, have been shown to promote multiple addiction-relevant phenotypes, including enhanced motivation for drug and increased relapse vulnerability despite lower overall drug consumption. While both schedules produce robust behavioral adaptations, it remains unclear whether addiction-relevant outcomes are determined primarily by the current schedule of drug availability or shaped by early plasticity mechanisms established during initial drug exposure. These experiments test whether addiction-like behaviors induced by distinct patterns of cocaine availability remain flexible following changes in access

conditions or persist despite alterations in the drug-taking environment. To address this question, male and female Long-Evans rats were trained to self-administer either cocaine or sweetened condensed milk (SCM) in either long-access (5 h continuous access) or intermittent-access (5 h; alternating 5 min of reward availability and 25 min non-availability) sessions for 11 days. Motivation for reward was assessed using a progressive ratio procedure, and compulsive-like responding was evaluated using punished self-administration. Rats were then switched to the alternate access condition for an additional 10 days and retested. Additionally, cue-induced reward seeking was assessed following 1 and 45 days of abstinence to evaluate craving-like behavior. Preliminary analyses suggest that behavioral adaptations depend on both reward type and access history. While access schedule influenced patterns of reward intake, cocaine- and SCM-reinforced animals appeared to differ in their responses to schedule transitions. Ongoing analyses are evaluating the relative contributions of early and recent reward experience to motivation, compulsive-like behavior, and incubation of craving. These findings suggest that the behavioral consequences of drug exposure may depend not only on the current environment of drug availability but also on the history of drug access that preceded it. Determining how prior and recent drug-taking experiences interact to shape addiction-relevant behaviors may provide new insight into the mechanisms through which patterns of drug use influence vulnerability to compulsive drug seeking and relapse.

Disclosures: K.M. Williford: None. **I.D. Daly:** None. **A. Shin:** None. **E. Guan:** None. **S. Kim:** None. **H. Love:** None. **S. Magnus:** None. **H. Rolls:** None. **A. Serratos:** None. **S.M. Groman:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.08/KK20

Topic: H.08. Drugs of Abuse and Addiction

Support: Hope for Depression Research Foundation
NIMH Grant P01DA047233
F99 Grant to A.M.T.

Title: Effects of Chronic Cocaine Exposure on Approach/Avoidance Decision-Making

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Abstract: Approach/avoidance (A/A) conflicts require balancing the pursuit of rewards with the potential for undesirable outcomes. Neuropsychiatric disorders, such as drug abuse, can alter the balance of A/A decision-making, leading to maladaptive behaviors such as risky approaches to drug and natural rewards. Despite the prevalence of these disruptive A/A dynamics, the

mechanism underlying the interaction between drug exposure and natural reward-seeking during A/A conflict is poorly understood. Here, we employed a platform-mediated avoidance paradigm, where we conditioned mice to avoid tones paired with foot-shocks by stepping onto a platform, thereby forfeiting access to saccharine-water rewards. We then exposed them to chronic cocaine or saline injections (20mg/kg intraperitoneal) for five days. Following a 5-day drug-free period, we tested their approach and avoidance responses under extinction conditions, where mice are exposed to tones associated with foot-shock with no consequences. Our results indicate that chronic cocaine—but not saline—exposure selectively modulates A/A behavior by increasing reward-seeking and reducing avoidance during tone periods, as opposed to inter-tone periods. These findings suggest that chronic cocaine alters decision-making processes by biasing behavior toward reward-seeking. To investigate the neurobiology underlying this heightened reward-seeking that facilitates avoidance extinction, we employed a combination of brain immunolabeling and 3D-volume imaging via iDISCO+, RNAScope, and viral-mediated gene transfer. Our preliminary iDISCO+ results revealed that chronic cocaine induces widespread ΔFOSB expression, including in the nucleus accumbens (NAc) and prefrontal cortex (PFC). ΔFOSB is a transcription factor known to be a key mediator of addiction-like phenotypes. Ongoing experiments aim to dissect the circuitry by selectively manipulating levels of endogenous ΔFOSB in NAc and PFC neurons expressing dopamine D1 or D2 receptors, which are known to signal A/A decision-making differentially. Our study provides insight into the neurobiological mechanisms underlying cocaine-induced changes in key decision-making biases, shedding light on cell-autonomous mechanisms that signal these behavioral responses. Supported by the National Institute on Drug Abuse

Disclosures: C. Blaschke: None. **T. Markovic:** None. **E.J. Nestler:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.09/KK21

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant K01DA054306
BBRF Young Investigator Grant 2024

Title: Modeling Approach-Avoidance Conflict during Cocaine Self-Administration in Rats

Authors: *R. G. FILENI[1,2], S. BANAL[1,2], I. RODRIGUEZ-LAUSELL[1,2], R. AGGARWAL[1,2], T. GOOLD[1], D. SPARKS[1], F. J. MARTINEZ-RIVERA[1,2];
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Abstract: Substance-use disorders are associated with deficits in decision-making that contribute to persistent drug use despite negative consequences. While other studies have used inescapable footshock paradigms to differentiate passive abstinence from punishment-resistant drug seeking,

they do not capture the active decision between approaching a reward or avoiding harm. To instead model active approach-avoidance decisions, we have developed an active avoidance task based on the platform-mediated avoidance (PMA) paradigm in which access to cocaine reward competes with the motivation to avoid a footshock. Male rats are first trained under a high-demand reinforcement schedule and then undergo approach-avoidance trials in which cocaine access is paired with a predictable and avoidable footshock. Findings indicate that after 10 days of repeated training, two distinct avoidance phenotypes emerge: roughly half of rats display robust avoidance (Avoiders), while the other half of rats consistently fail to avoid the shock (Non-Avoiders). Further, both phenotypes show no differences in drug-seeking both during acquisition and during the PMA task, suggesting that individual differences in drug-seeking fail to explain avoidance behavior. To investigate what molecular adaptations underly these differences in avoidance behavior, ongoing analyses aim to identify the transcriptomic signatures and c-Fos expression (activity marker) of Avoiders and Non-Avoiders in key regions associated with decision-making such as the prelimbic cortex. Together, we present a novel behavioral task that can reveal individual differences in drug-associated approach-avoidance decisions that may have relevance as a preclinical model for impaired decision-making in substance-use disorders.

Disclosures: R.G. Fileni: None. **S. Banal:** None. **I. Rodriguez-Lausell:** None. **R. Aggarwal:** None. **T. Goold:** None. **D. Sparks:** None. **F.J. Martinez-Rivera:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.10/KK22

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant K01DA054306
Brain Behavior Research Foundation

Title: Transcriptional signatures associated with cocaine renewal and reacquisition

Authors: *I. RODRIGUEZ-LAUSELL[1], R. AGGARWAL[1], P. NAGENDIRAKUMAR[1], R. FILENI[1], T. M. GOOLD[1], S. CHEN[2], F. J. MARTINEZ-RIVERA[1];
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Abstract: Renewal and reacquisition (R/R) of drug-associated memories contribute to relapse. Although extinction training has shown limited effectiveness in reducing relapse, understanding its underlying neurobiological mechanisms may reveal strategies to enhance its efficacy. The nucleus accumbens (NAc), a key region of the brain reward circuitry, has been implicated in R/R; however, its transcriptional regulation during relapse-related behaviors has yet to be fully characterized. Here, we used a rat model of contextual cocaine self-administration (SA), where animals self-administered cocaine in one context (A), underwent extinction training in a different context (B) or home-cage withdrawal, and were subsequently re-exposed to context A in the

absence (renewal), then presence (reacquisition) of the drug. We found that extinction training produced a significant reduction in cocaine-seeking behavior during renewal compared to home-cage withdrawal. Notably, extinction-trained rats also exhibited delayed reacquisition, suggesting a persistent protective effect of extinction learning on relapse. To investigate the molecular mechanisms underlying these behavioral effects, we performed transcriptomic analyses of the NAc core and shell subregions. Ongoing analyses are expected to reveal distinct patterns of gene expression associated with contextual extinction and cocaine-seeking behaviors. Together, these findings demonstrate the impact of context-based extinction in attenuating cocaine-associated renewal and delaying reacquisition, while also highlighting potential transcriptional modifications within NAc subregions that are important for R/R.

Disclosures: I. Rodriguez-Lausell: None. **R. Aggarwal:** None. **P. nagendirakumar:** None. **R. Fileni:** None. **T.M. Goold:** None. **S. Chen:** None. **F.J. Martinez-Rivera:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.11/KK23

Topic: H.08. Drugs of Abuse and Addiction

Support: PA-20-185

Title: Encoding of Cocaine Seeking and Demand in the Prelimbic Cortex to Dorsomedial Striatum (PL-DMS) Circuit

Authors: *P. A. FOGEL;
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Abstract: Individuals with substance use disorder often continue drug use despite mounting adverse consequences, yet the neural mechanisms governing sensitivity to these costs remain unclear. We hypothesized that activity within the prelimbic cortex to dorsomedial striatum (PL-DMS) circuit contributes to the evaluation of reward-associated costs and may influence persistence in cocaine seeking. To test this, male and female Sprague Dawley rats were injected with a Cre-dependent GCaMP6s AAV to allow for *in vivo* calcium imaging of the PL-DMS circuit in costly self-administration behaviors. Animals experienced two types of self-administration (effortful and punished) where the respective cost systematically increased within each session. Manipulations to cost during effortful self-administration tasks included a systemic increase of the reinforcement schedule, while punished self-administration included a reward-paired intravenous infusion of histamine of increasing duration throughout the tasks. Behavioral economic metrics were used to analyze how demand for cocaine may change across various types and magnitude of costs. Preliminary findings demonstrate the emergence of distinct neural activity patterns associated with reward type and cost, specifically sucrose-, cocaine-, and punishment-sensitive groups. Behavioral economic analyses indicate reduced sensitivity to

punishment during cocaine seeking relative to sucrose seeking, whereas effort-based costs exerted similar effects across reward types. Together, these findings suggest that PL-DMS circuitry encodes information relevant to cost-benefit evaluation and may contribute to maladaptive persistence in drug seeking despite negative consequences.

Disclosures: P.A. Fogel: None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.12/KK24

Topic: H.08. Drugs of Abuse and Addiction

Support: 1R01DA058653-01A1

Title: Encoding of Effortful and Punished Costs in the Prelimbic-Accumbens Pathway During Cocaine Self-Administration and Response to 4-ACO-DMT

Authors: *R. SOSA JURADO, M. ESPINOSA SALGADO, T. M. MOSCHAK;
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Abstract: Cocaine use disorder (CUD) is a debilitating condition characterized by compulsive drug-taking despite escalating cost and lacks approved pharmacotherapy. Effortful and punished costs represent computationally distinct problems that dissociate behaviorally and neurally after chronic cocaine, yet how prelimbic cortex to nucleus accumbens core (PrL to NAc core) projections encode these cost modalities is unknown. To investigate cost arbitration under cocaine, adult male and female Long-Evans rats performed two progressive behavioral economic assays: an Effortful Self-Administration (ESA) task using a within-session progressive ratio design increasing effort along a quarter-log scale, and a Punished Self-Administration (PSA) task pairing cocaine infusions (0.33 mg/infusion) with graded histamine doses. Sucrose self-administration served as a natural reward control. These tasks produce continuous measures of behavioral flexibility (alpha), reflecting cost sensitivity and motivational rigidity. In vivo calcium imaging of PrL to NAc core projections via Cre-dependent GCaMP in PrL with retrograde Cre in NAc core captured projection-specific dynamics during both cost conditions. We additionally examine whether a single dose of 4-ACO-DMT, a serotonergic tryptamine acting at the 5-HT2A receptor, alters cost-based cocaine self-administration and PrL to NAc core activity. Preliminary behavioral data (N = 3) indicate nosepoke responding differed significantly between cocaine and sucrose self-administration ($t(2) = 3.12$, $p = 0.045$). Calcium imaging data was collected from PrL to NAc core projections during costly self-administration. These exploratory data demonstrate that the behavioral economic paradigm captures distinct cocaine versus natural reward response profiles during self-administration.

Disclosures: R. Sosa Jurado: None. **M. Espinosa Salgado:** None. **T.M. Moschak:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.13/KK25

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA046457

Title: Lateral striatum: Distinct from DLS in cocaine-seeking function and midbrain input

Authors: *E. BRILL[1], P. GOPAL[2], S. HANDEL[3], R. J. SMITH[4];
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Abstract: In an animal model of compulsive drug seeking, a subset of rats continue to self-administer cocaine despite footshock and are considered punishment resistant. Our lab has found that punishment resistance is associated with inflexible habits. Accordingly, inactivation of the dorsolateral striatum (DLS, which is necessary for habits) via lesions or AMPA antagonists led to enhanced punishment sensitivity, implicating the DLS in punishment resistance. Interestingly, lesions of the lateral striatum, the area located just ventral to the DLS, had the opposite effect and enhanced punishment resistance. These findings suggest that the lateral striatum may have functions distinct from other striatal subregions. To investigate this further, we compared striatal subregions in terms of punishment-induced c-Fos expression, as well as retrogradely-traced inputs from midbrain dopamine regions. When we examined c-Fos activity related to punishment of cocaine seeking, we found that c-Fos expression in the lateral striatum was positively correlated with the number of trials completed under punishment. In contrast, we found no significant correlations in the DLS or dorsomedial striatum (DMS). When we compared retrograde inputs to striatal subregions, we found differences in cell body locations in the substantia nigra compacta (SNc). Cells that projected to the lateral striatum were located dorsolaterally to those projecting to DMS and DLS. These anatomical findings contradict the expected dorsal/ventral organization, indicating that midbrain inputs do not follow a simple dorsal/ventral gradient. Together, these data support the idea that the lateral striatum may function as a distinct subregion in the striatum with unique anatomical and functional properties. Ongoing studies are further testing the involvement of the lateral striatum in punishment responding.

Disclosures: E. Brill: None. **P. Gopal:** None. **S. Handel:** None. **R.J. Smith:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.14/KK26

Topic: H.08. Drugs of Abuse and Addiction

Title: The Role of Lateral Entorhinal Cortex in Natural Reward and Cocaine Cue Memories

Authors: *S. MOUSAVI[1], M. ALADSANI[2], R. MIRKHELKER[3], A. L. EAGLE[4];
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Abstract: Relapse in cocaine use disorder is strongly driven by environmental cues that reactivate drug-associated memories, yet the neural circuits underlying cue-induced reward seeking remain incompletely understood. The lateral entorhinal cortex (LEC) plays a critical role in associative memory processing and sends direct projections to the nucleus accumbens (NAc), which suggests that LEC-NAc circuit may contribute to cue-reward encoding and relapse vulnerability. To investigate this, we used fiber photometry to record calcium activity in the LEC during exposure to natural and drug reward-predictive cues. Adult C57BL/6J mice were tested for LEC activity during natural reward (sucrose) and cocaine-associated cue presentation, in separate cohorts. The LEC was infused with a non-cell-specific recombinant virus expressing GCaMP, and calcium signals were recorded during sucrose or cocaine self-administration, extinction, and cue-induced reinstatement. We found that mice acquired natural reward and cocaine self-administration, reduced responding during extinction, and reinstated responding following cue presentation. Fiber photometry revealed significantly higher calcium-dependent activity with event-related increases surrounding cocaine-predictive cues. We also tested mice for immediate early gene (IEG) activation of LEC neurons in response to natural reward (sucrose) and cocaine cues. Mice underwent sucrose or cocaine self-administration and extinction. Mice were then separated into 3 groups: Cues (those that underwent reinstatement paired with sucrose/cocaine cues), No Cues (those that were placed into the reinstatement context without cues), and Homecage (those mice that were left in their homecage instead of being tested for reinstatement). Findings reveal that both natural reward cues and cocaine cues increase IEG activation in LEC neurons. Together, these results show that the LEC is engaged by reward-predictive cues during cocaine reward seeking and provide a foundation for future work to determine whether NAc-projecting LEC neurons are also recruited during cue-induced reinstatement of cocaine seeking.

Disclosures: S. Mousavi: None. **M. AlAdsani:** None. **R. Mirkhelker:** None. **A.L. Eagle:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.15/KK27

Topic: H.08. Drugs of Abuse and Addiction

Support: K01DA055068
Mercer Startup
Mercer Navicent Grant
Mercer Provost Grant

Title: Is Context Driven Recruitment of mPFC Fos Ensembles Sufficient to Support Cocaine Seeking?

Authors: *A. J. V. CAROLAND-WILLIAMS[1], A. GHEIDI[2];
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Abstract: Relapse in substance use disorder is strongly driven by drug-associated contexts and cues1, yet the neuronal populations underlying this process remain incompletely defined2. We used Fos-lacZ transgenic rats and Daun02 inactivation to target medial prefrontal cortex (mPFC) neurons recruited during context re-exposure following cocaine self-administration and forced abstinence3. Selective inactivation of these neurons reduced active lever responding during re-exposure, reflected by diminished discrimination between active and inactive levers, while Daun02 induction produced a marked increase in ablation of Fos-expressing neurons recruited during cue and context-associated reward seeking. These findings demonstrate that context-driven recruitment of mPFC ensembles is sufficient to engage neuronal populations that support cocaine seeking4, and that disruption of these ensembles attenuates relapse-like behavior.

Disclosures: A.J.V. Caroland-Williams: None. **A. Gheidi:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.16/KK28

Topic: H.08. Drugs of Abuse and Addiction

Support: 5R01DA049139-05

Title: The effects of theta-like stimulation of the infralimbic cortex on cocaine seeking during extinction in rats

Authors: *K. V. FLINN, R. T. LALUMIERE;
Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Evidence suggests that the rat infralimbic cortex (IL) inhibits drug seeking during the extinction of cocaine self-administration. Additionally, clinical work indicates that theta oscillations within the prefrontal cortex may be associated with inhibitory control. Previous work

in our laboratory examining local field potential activity within the IL found an association between maintained theta (4-10 Hz) power within the IL and the suppression of cocaine seeking during extinction. In contrast, IL theta power decreased prior to a lever press during extinction, suggesting a potential role for such theta activity in the inhibition of cocaine seeking. Therefore, we examined whether optogenetic stimulation of the IL at a theta-like rhythm (8 Hz) would suppress cocaine-seeking behavior during extinction. Sprague-Dawley rats were given bilateral intra-IL AAV injections to express either the excitatory opsin ChR2(E123A) or a control eYFP vector as well as bilateral optical fiber implants aimed at the IL. Rats then underwent cocaine self-administration during daily 6-h sessions for a minimum of 12 d. During the sessions, the levers were available during discrete 30 s windows. An active lever press produced an infusion of cocaine (0.33 mg/kg/infusion) as well as 5 s light and tone cues and lever retraction. Next, rats underwent 5 d of extinction training, wherein a lever press no longer resulted in a cocaine infusion or cues. Laser illumination (473 nm, 8 Hz, 5 ms pulse width) was given 5 s before lever extension and continued until lever retraction or a lever press, resulting in a maximum duration of 35 s of stimulation. Rats then underwent 5 d of extinction training in which they received no laser illumination. For the next 10 d, rats underwent cued extinction training, in which a lever press resulted in the presentation of light and tone cues previously associated with a cocaine infusion but no cocaine infusion. As before, laser illumination was provided for the first 5 d only. Preliminary results suggest that IL stimulation reduced lever pressing during cued extinction and increased the latency to lever press within a trial during cued extinction. Studies are ongoing to confirm these findings.

Disclosures: K.V. Flinn: None. **R.T. LaLumiere:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.17/KK29

Topic: H.08. Drugs of Abuse and Addiction

Support: DA031115
MH053851

Title: Role of the orbitofrontal cortex in reinstatement of drug seeking

Authors: *K. M. TUITE[1], D. R. MAGUIRE[2], D. A. MORILAK[2,3];
[2]Pharmacol., [1]UT Hlth. San Antonio, San Antonio, TX; [3]South Texas Veterans Hlth. Care Service, San Antonio, TX

Abstract: Cocaine use disorder (CUD) is increasingly prevalent in the United States and is characterized by high rates of relapse. There are no FDA-approved treatments for CUD and cocaine is increasingly involved in overdose deaths, making it a major public health concern. The orbitofrontal cortex (OFC) becomes hyperactive over the course of CUD and the degree of

activation of the OFC is correlated with craving severity. In rodents, OFC inactivation prevents reinstatement of cocaine and opioid seeking, a model for relapse. Additional studies indicate that activation of the OFC increases reinstatement responding when animals have intermittent access to cocaine. In this study, we utilize a within-subject design to activate the OFC during reinstatement to test the hypothesis that OFC activation will increase responding during reinstatement. Male and female Sprague-Dawley rats were implanted with femoral vein catheters to self-administer cocaine (0.32 mg/kg/infusion) during 90-minute sessions. Animals also received injections of Gq excitatory DREADDs bilaterally into the OFC. Following 1-2 weeks of training for acquisition of cocaine self-administration, rats underwent repeated 3-day cycles of self-administration, extinction, and reinstatement tests. The first cycle involved an initial baseline reinstatement test in which animals received saline pretreatment i.v. and water vehicle i.p. and infusions of saline upon completion of the response requirement. Next, animals received injections of Compound 21 (C21, 1 mg/kg i.p.) 15 minutes preceding reinstatement testing and varying doses of cocaine (0.1-1.0 mg/kg i.v.) 5 minutes before testing. OFC activation by C21 alone increased the rate of responding and total number of responses compared to vehicle control during reinstatement. The effects of OFC activation were more pronounced during reinstatement tests following cocaine pretreatment. These data indicate that OFC activation alone induces drug seeking which could combine with other stimuli known to reinstate drug seeking (drug, cues, or stress) to increase the risk of relapse. In animals responding for sucrose, we expect no effect of DREADD based on results from previous literature showing no effect of OFC manipulations on responding for food. These results demonstrate that OFC activation is sufficient to produce increases in drug seeking behaviors, specifically enhancing the return to behavior acquired prior to extinction. The effect of OFC activation on reinstatement is consistent with previous literature regarding OFC dysfunction promoting perseverative behavior. Ongoing studies will test the generalization of these effects to food reinforcement.

Disclosures: K.M. Tuite: None. **D.R. Maguire:** None. **D.A. Morilak:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.18/KK30

Topic: H.08. Drugs of Abuse and Addiction

Support: NIA 1RF1AG071683
Adelson Medical Research Foundation
NIDA R01DA047441
NIDA R01DA047981
NIDA F32DA055438
George Hewitt Foundation

Title: Altered medial habenula GABA-related gene expression following reinstatement of cocaine self-administration in mice

Authors: *J. CHILDS;
Marshall Univ., Huntington, WV

Abstract: Relapse vulnerability is driven in part by persistent maladaptive drug-associated memories formed during drug use. These memories underlie relapse triggers such as drug-associated cues and contexts and are thought to involve stable adaptations within neural circuits regulating motivated behavior. While recent studies have begun to implicate the medial habenula (MHb) in cocaine-associated behaviors, the mechanisms by which the MHb contributes to reinstatement of cocaine seeking remain poorly understood. Our recent work identified a critical role for the epigenetic effector gene Nr4a2 within MHb cholinergic neurons in reinstatement of cocaine intravenous self-administration (IVSA). Using viral-mediated dominant negative Nr4a2 expression, we found that disruption of Nr4a2 signaling in MHb cholinergic neurons attenuated reinstatement behavior. In complementary studies, chemogenetic activation of MHb cholinergic neurons was sufficient to drive reinstatement-like behavior, while fiber photometry recordings demonstrated substantially elevated MHb cholinergic neuron activity during reinstatement testing compared to acquisition and extinction of cocaine conditioned place preference. To identify molecular adaptations associated with reinstatement, we performed single nucleus RNA sequencing on habenula tissue collected following reinstatement of cocaine IVSA. Reinstatement produced widespread transcriptional alterations across MHb neuronal and glial populations. Because the large number of differentially expressed genes complicated interpretation of the dataset, we next performed weighted gene co-expression network analysis to identify coordinated transcriptional modules associated with reinstatement. Gene ontology analysis revealed enrichment of modules linked to addiction-related pathways including opioid, nicotine, and amphetamine signaling, as well as GABAergic and endocannabinoid signaling pathways known to regulate MHb activity. Within the most behaviorally relevant transcriptional modules, we identified several overlapping hub genes encoding GABA receptor subunits and GABA-associated proteins, suggesting that altered GABAergic signaling may represent a key mechanism by which the MHb regulates relapse-related behaviors. Ongoing studies are testing causal relationships between reinstatement-associated changes in MHb GABA receptor signaling, MHb neuronal activity, and cocaine-associated behaviors using RNA Scope, viral-mediated gene manipulation, fiber photometry, and cocaine IVSA models.

Disclosures: J. Childs: None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.19/KK31

Topic: H.08. Drugs of Abuse and Addiction

Title: Ketamine Reshapes mPFC Inhibition After Cocaine Memory Retrieval in Female Rats

Authors: *S. MODABERI[1,2], M. ISLAM[2], B. A. SORG[4], S. T. HENTGES[3], T. E. BROWN[2]; [2]Integrative Physiol. and Neurosci., [3]Integrative Physiol. & Neurosci., [1]Washington State Univ., Pullman, WA; [4]Neurobio., Legacy Res. Inst., Portland, OR

Abstract: Cocaine use disorder remains a major public health concern, with women showing faster progression to dependence and greater relapse vulnerability than men. Drug-associated memories can be weakened when retrieval triggers prediction-error-driven destabilization, opening a reconsolidation window during which memories become susceptible to modification. This process is governed by medial prefrontal cortex (mPFC) circuits that recruit parvalbumin-positive fast-spiking interneurons (FSIs). In males, ketamine administered prior to novel cocaine memory reactivation suppresses subsequent cocaine seeking, but whether this effect extends to females remains unknown. Here, we tested whether ketamine paired with novel memory retrieval alters cocaine memory updating in female rats. Animals underwent cocaine self-administration on a fixed-ratio1 (FR1) schedule followed by a variable-ratio5 (VR5) retrieval session designed to induce prediction error. Rats received ketamine (6 mg/kg, i.p.) or saline prior to retrieval; an additional control group remained on FR1. Whole-cell patch-clamp recordings were obtained from mPFC neurons 24h later. Novel retrieval increased responding in both VR5 (62.23 ± 33.26, p=0.0005) and VR5+ketamine (56 ± 20.10, p=0.018) groups relative to FR1 (16.20 ± 6.19), but ketamine did not alter responding or infusion number during retrieval itself. We observed no ketamine-related differences in intrinsic excitability of FSIs or pyramidal neurons. However, ketamine-paired retrieval reduced the frequency (VR5+ketamine, 0.51 ± 0.47, VR5, 2.13 ± 1.08, FR1=2.36 ± 1.68, p=0.02) and trended towards a reduction in the amplitude (VR5+ketamine, 21.39 ± 5.38, VR5, 32.94 ± 8.15, FR1=31.62± 8.27, p=0.06) of spontaneous inhibitory postsynaptic currents (sIPSCs) onto pyramidal neurons, indicating decreased inhibitory synaptic input. These findings suggest that ketamine engages post-retrieval plasticity mechanisms without disrupting retrieval performance, addressing a critical gap in understanding relapse vulnerability in females.

Disclosures: S. Modaberi: None. **M. Islam:** None. **B.A. Sorg:** None. **S.T. Hentges:** None. **T.E. Brown:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.20/KK32

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant: 5R01DA056193-04

Title: Intermittent access to cocaine disrupts sleep architecture during prolonged abstinence

Authors: *S. R. COHEN[1], V. MIGOVICH[3], P. CLARK[3], R. A. ESPAÑA[2];
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Abstract: Individuals who struggle with cocaine use disorder display sleep dysregulation, often marked by reductions in rapid eye movement (REM) sleep and increased REM sleep fragmentation that persist throughout abstinence. We recently demonstrated that intermittent access to cocaine increases dopamine uptake rate and dopamine transporter sensitivity to cocaine following a period of abstinence - despite similar total cocaine intake levels between the two schedules. Further, we demonstrated that intermittent access to cocaine promotes REM sleep disruptions early in abstinence that increase throughout a prolonged abstinence period. To remedy this REM sleep deficit, we recently implemented a sleep restoration paradigm early in abstinence and successfully mitigated the effects of intermittent access to cocaine during abstinence. In these studies, we assessed if these acute effects of sleep restoration were maintained after a prolonged 28-day abstinence period. We hypothesized that normalizing REM sleep early in abstinence would prevent the development of incubation of cue-induced cocaine seeking and aberrant dopamine transporter adaptations later in abstinence. Following a baseline sleep/wake recording, rats self-administered cocaine and were then subjected to a cue-induced seeking test on the first and last days of abstinence. Following the first seeking test, rats returned to their sleep recording chambers and either did or did not receive sleep restoration for the next six days. Finally, we measured if sleep restoration normalized dopamine transporter adaptations using fast scan cyclic voltammetry on day 29 of abstinence. Preliminary results indicate that the short-term sleep restoration paradigm indeed reverses the effects of intermittent access to cocaine up to 28 days of abstinence. Together, these findings demonstrate the need for early intervention in restoring sleep/wake architecture during abstinence from cocaine.

Disclosures: S.R. Cohen: None. **V. Migovich:** None. **P. Clark:** None. **R.A. España:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.21/KK33

Topic: H.08. Drugs of Abuse and Addiction

Title: Novel Cocaine Memory Reactivation After Ketamine Alters GABAergic Tone onto Prefrontal Pyramidal Neurons and Reduces Drug Seeking Behavior

Authors: *M. ISLAM[1], S. MODABERI[1], B. A. SORG[4], S. T. HENTGES[2], T. E. BROWN[3];
[2]Integrative Physiol. & Neurosci., [3]Integrative Physiol. and Neurosci., [1]Washington State Univ., Pullman, WA; [4]Neurobio., Legacy Res. Inst., Portland, OR

Abstract: Cocaine use disorder is driven in part by persistent drug-associated memories that promote relapse. The medial prefrontal cortex (mPFC) plays a central role in regulating drug-

seeking behavior, yet the circuit mechanisms underlying this control remain poorly defined. Within the mPFC, excitatory pyramidal neurons (PYR) are tightly regulated by parvalbumin-positive fast-spiking interneurons (FSIs), which gate cortical output and constrain behavioral responses. Recent work from our group demonstrated that ketamine administration in male rats prior to a novel memory retrieval session attenuated subsequent cocaine-seeking, consistent with disrupted memory reconsolidation. However, the synaptic and intrinsic electrophysiological adaptations within this post-retrieval window remain unknown. Here, we tested whether ketamine-mediated disruption of cocaine memory reconsolidation alters intrinsic excitability and inhibitory synaptic input onto mPFC neurons. Male rats underwent cocaine self-administration under a fixed-ratio 1 (FR1) schedule followed by a variable-ratio (VR5) retrieval session. Animals received ketamine (6 mg/kg, i.p.) or saline immediately prior to retrieval, while an additional control group remained on the FR1 schedule. Whole-cell patch-clamp recordings were performed 24h after memory retrieval. Intrinsic membrane properties did not differ across groups for any measure assessed, including input resistance, resting membrane potential, rheobase, firing rate, and capacitance in either FSIs or PYRs, indicating stable baseline intrinsic excitability. In contrast, preliminary studies suggest that synaptic transmission onto PYR neurons shifted significantly. Ketamine administration induced an increase in spontaneous inhibitory postsynaptic current (sIPSC) frequency compared to VR5 controls (FR1: 3.95±1.96 Hz; VR5: 1.88±1.83 Hz; VR5+Ketamine: 6.37±4.14 Hz; $p=0.0046$) and a significant increase in sIPSC amplitude (FR1: 33.48±8.79 pA; VR5: 30.66±9.80 pA; VR5+Ketamine: 44.83±5.25 pA; $p=0.0492$), as assessed by one-way ANOVA with post-hoc comparisons. Event kinetics, including rise and decay times were unaffected. These findings demonstrate that ketamine-mediated disruption of cocaine memory reconsolidation in males is characterized by an acute escalation of local synaptic inhibition onto mPFC output neurons rather than alterations in baseline intrinsic excitability. By revealing an upregulation of GABAergic drive during memory destabilization, these data provide a novel synaptic framework for how ketamine interventions modulate prefrontal circuits to disrupt drug-associated memories.

Disclosures: M. Islam: None. **S. Modaberi:** None. **B.A. Sorg:** None. **S.T. Hentges:** None. **T.E. Brown:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.22/KK34

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA031900
NSF GRFP 2041772

Title: Characterizing hypocretin/orexin neuron involvement in incubation of cocaine craving

Authors: *S. B. SAMELS[1], Z. D. BRODNIK[2], C. SILLER-PEREZ[3], E. C. ANDRADE[3], R. M. SEARS[3], R. A. ESPAÑA[2];
[1]Neurobio. and Anat., Drexel Univ. Col. of Med. Neurosci. Program, Philadelphia, PA; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Emotional Brain Inst., Nathan Kline Inst., Orangeburg, NY

Abstract: One of the major challenges for treating substance use disorders is the progressive intensification, or "incubation", of drug craving and seeking that emerges during abstinence and that contributes to relapse. The hypocretin/orexin neuropeptide system regulates reward processes, and recent evidence indicates that blocking hypocretin receptors prevents the incubation of cocaine seeking. To date, however, it remains unknown whether hypocretin neurons themselves dynamically track cocaine-seeking behavior across abstinence. Here, we tested to what extent hypocretin neuron activity contributes to the expression of incubation of cocaine seeking by using fiber photometry to measure hypocretin Ca^{2+} transients during behavior. Rats self-administered on either intermittent access to cocaine, which produces robust incubation, or short access self-administration, which does not produce incubation. All rats underwent 28 days of abstinence where we recorded hypocretin neuron activity during cue-induced seeking tests on the first and last days of abstinence. Preliminary results suggest that hypocretin neurons exhibited robust, time-locked activity during cue-induced approach and responding across both self-administration schedules. However, only intermittent access rats showed sustained transient magnitudes across abstinence, whereas short access rats displayed attenuated activity at the later abstinence timepoint. These findings indicate that hypocretin neurons may track or differentiate between incubated and non-incubated seeking, which identifies hypocretin signaling as a potential mechanism underlying relapse vulnerability.

Disclosures: S.B. Samels: None. **Z.D. Brodnik:** None. **E.C. Andrade:** None. **R.M. Sears:** None. **R.A. España:** None.

Poster

PSTR244: Cocaine: Reinforcement, Seeking, Reinstatement, and Memory

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR244.23/KK35

Topic: H.08. Drugs of Abuse and Addiction

Support: 1R03DA060344-01

Title: Devaluing memories of cocaine reward with semaglutide leads to reductions in the motivation to seek out and self-administer cocaine in rats

Authors: *B. MO[1], M. SANTOS[2], K. HILL[3], L. S. VOUTOUR[4], V. J. BRAMAN[1], A. W. JOHNSON[5];
[1]Michigan State Univ., East Lansing, MI; [2]Michigan State Univ., Macomb, MI; [3]Michigan State

Univ., Clarkston, MI; [4]Michigan State Univ., East Lansing, MI, ; [5]Psychology, Michigan State Univ., East Lansing, MI

Abstract: Substance use disorder is characterized by persistent drug seeking and excessive motivation to obtain drugs despite adverse consequences. Previous work from our laboratory demonstrated that pairing the memory of cocaine reward with gastric malaise produced by LiCl substantially reduced cocaine-seeking behaviors. However, in humans the use of LiCl is both uncommon and ethically challenging, which limits the translational potential of our approach. Semaglutide is a clinically approved glucagon-like peptide-1 (GLP-1) receptor agonist and its side-effects can include nausea and gastric malaise. Accordingly, in this study we examined whether semaglutide could be used to evoke mediated devaluation and disrupt the motivation to seek out and self-administer cocaine. Male Sprague Dawley were implanted with jugular catheters followed by cocaine self-administration training sessions where each active lever response led to a cocaine infusion and presentation of a light/tone conditioned stimulus (CS). Following training, rats were placed into a distinct aversion context and the CS was presented (to retrieve cocaine reward memories) followed by a single 0.1 mg/kg injection of semaglutide or saline. Rats were later tested for cocaine-seeking under extinction conditions as well as motivation to obtain cocaine using a progressive ratio test. Strikingly, relative to saline controls, CS-semaglutide group exhibited reduced active lever responding during the cocaine seeking test, and a substantial reduction in cocaine intake and reduced break point during the progressive ratio test. Importantly, these effects required pairing of the CS-evoked memory of cocaine with semaglutide as injections of the GLP-1 receptor agonist alone did not disrupt cocaine seeking behaviors. These findings suggest that mediated devaluation through semaglutide can be used as a translationally relevant approach to disrupt cocaine-seeking behaviors and may reflect a disruption in dopamine signaling in mesolimbic reward circuitry.

Disclosures: B. Mo: None. **M. Santos:** None. **K. Hill:** None. **L.S. Voutour:** None. **V.J. Braman:** None. **A.W. Johnson:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.01/KK36

Topic: I.01. Attention

Support: Brigham Young University's John A. Widtsoe Grant

Title: The Impact of Habitual Social Media Usage on Episodic Memory

Authors: *S. STORM[1], J. MCFARLANE[2], J. A. NIELSEN[3];
[1]Brigham Young University, Dept. of Neurosci., Provo, UT; [2]Neurosci., [3]Psychology, Brigham Young Univ., Provo, UT

Abstract: Despite the continued rise in social media usage, much is still unknown about the impact of long-term social media use on human cognition. In this study, we aimed to uncover the effects of habitual social media use on human episodic memory. Participants were excluded based on neurological and psychiatric conditions, history of brain injury, English non-fluency, and colorblindness. We utilized a time-tracking app called Stay Free to collect two weeks of mobile device social media use data from healthy young adults (n=167, 106 female; age 18-25, avg. 20.6). We then compared their average daily social media consumption (minutes and sessions per day) to their scores on an episodic memory task called the Mnemonic Similarity Task (MST). Our multiple linear regression model showed that a higher average number of social media sessions per day during the two week data collection period was associated with significantly reduced performance on the MST (P=0.009). We concluded that increased frequency of social media consumption across a two-week period is associated with decreased episodic memory abilities. Future research should focus on whether social media use differentially impacts vulnerable populations (such as individuals with ADHD).

Disclosures: S. Storm: None. **J. McFarlane:** None. **J.A. Nielsen:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.02/KK37

Topic: I.01. Attention

Title: The Impact of Habitual Short-Form Social Media Use on Sustained Attention

Authors: *A. LLOYD;
Brigham Young University, Dept. of Psychology, Provo, UT

Abstract: The Impact of Habitual Short-Form Social Media Use on Sustained Attention
Authors*Andrew Lloyd[1], Jared McFarlane[1], Jared Nielsen[2]; [1]Dept. Neuroscience, Brigham Young Univ., Provo UT, [2]Dept. Psychology, Brigham Young Univ., Provo UT**DisclosuresAndrew Lloyd**: None. **Jared McFarlane**: None. **Jared Nielsen**: None.**Abstract**In the past two decades, social media has gone from virtual essays and vacation posts to feeds with infinite hours of short-form content designed to take advantage of the brain's learning and reward system. Prior research shows that pre-short-form social media negatively effects human cognition in several aspects, including sustained attention, which makes the shift towards short-form media more disconcerting. If getting lost in posts and comparisons was enough to effect human attention, there is a concern that short-form content could have more dire effects. We recruited healthy young adults (n=167, 106 female; age 18-25, avg. 20.6) to download an app called StayFree which tracked social media usage on six different platforms (TikTok, Instagram, Facebook, Snapchat, X, and YouTube) for a two-week span. Participants were excluded based on neurological and psychiatric conditions, history of brain injury, English non-fluency, and colorblindness. After the data collection, the participants returned and we

administered the Sustained Attention to Response Task (SART) which measured sustained attention by tracking moments of mind-wandering and distraction. We utilized a multiple linear regression model to analyze the results of the SART which showed that social media habits during the two-week collection period were not indicative of varied reaction time on the SART (P=0.08). We concluded that social media consumption across a two-week period is not associated with inferior sustained attention in young adults. Further research should be conducted in a longitudinal aspect to see if extended social media use across several years, particularly during younger, developmental years, would have a greater effect on sustained attention. Continued research is also needed to investigate if long term and short-term social media use would have a measurable impact on more vulnerable populations such as those with ADHD.

Disclosures: A. Lloyd: None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.03/KK38

Topic: I.01. Attention

Support: Honda R&D Co., Ltd.

Title: Neural Correlates of Risk Judgment During Driving

Authors: *M. CHO[1], S. MURAKAMI[1], E. TSUMAYA[1], D. MATSUYOSHI[2], Y. YOMOGIDA[2], R. KANAI[2], Y. AIZAWA[3], M. YAMADA[3];
[1]Honda R&D Co., Ltd., Saitama, Japan; [2]ARAYA Inc., Tokyo, Japan; [3]Natl. Inst. for Quantum Sci. and Technol., Chiba, Japan

Abstract: Honda has set a goal of achieving zero fatalities from traffic accidents by 2050. To achieve this goal, it is essential to identify and minimize the causes of driver-related human errors. Previous studies have suggested that risk perception—the extent to which drivers perceive a traffic environment as dangerous—affects their subsequent driving behavior. In our previous analysis, drivers with higher risk perception performance exhibited smoother braking behavior and increased activity in area V4, a region associated with visual processing, when detecting other road users. In contrast, drivers with lower risk perception performance showed increased activity in the supramarginal gyrus, which is associated with bottom-up attention. However, little is known about the cognitive and neural processes involved in risk judgment based on perceived information, as well as those underlying individual differences in judgment performance. To investigate this, we recorded brain activity during the risk judgment task. We conducted an fMRI experiment in which participants were shown videos of driving scenes in a virtual environment generated by a driving simulator. They were asked to press a button whenever they perceived a situation in the video as dangerous. We evaluated drivers' risk perception performance based on

their responses in this experiment and examined its correlation with brain activity during risk judgment. The results showed that, during risk judgment, risk perception performance positively modulated activations in the left inferior frontal gyrus and left posterior temporal gyrus, whereas activity in the right angular gyrus and right precuneus showed a negative correlation. Previous studies have suggested that the left inferior frontal gyrus and left posterior temporal gyrus are involved in the controlled retrieval of semantic information, whereas the right angular gyrus and right precuneus are involved in the retrieval of mnemonic information during the early stage of episodic memory recall. These findings suggest that drivers who can appropriately evaluate risk possess semantic knowledge for risk prediction and make risk judgments by retrieving this knowledge, whereas drivers who cannot appropriately evaluate risk rely on recall of episodic memories rather than semantic knowledge.

Disclosures: M. Cho: A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **S. Murakami:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **E. Tsumaya:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **D. Matsuyoshi:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **Y. Yomogida:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **R. Kanai:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd.. **Y. Aizawa:** None. **M. Yamada:** 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.; Honda R&D Co., Ltd..

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.04/KK39

Topic: I.01. Attention

Support: Honda R&D Co., Ltd.

Title: Context-Based Risk Prediction Before Overt Gaze to Hazards in Simulated Driving

Authors: *S. MURAKAMI[1], M. CHO[1], D. MATSUYOSHI[2], Y. YOMOGIDA[2], R. KANAI[2], Y. AIZAWA[3], M. YAMADA[3];
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Abstract: Driving hazard detection may depend not only on low-level visual processing but also on the ability to use environmental context to predict risk and guide attention. In a previous analysis of the same fMRI dataset, using first gaze to the hazard as event onset, we found that a compensatory behavioral index (We defined this index as z-scored peripheral perceptual response time minus z-scored hazard-detection latency; larger values indicate slower peripheral perceptual responses but faster gaze allocation to hazards in the driving context) was associated with medial prefrontal cortex (mPFC) and inferior frontal junction (IFJ) activity, suggesting context-based risk interpretation and attentional control at the time of overt hazard inspection. However, neural processes preceding gaze allocation to hazards remain unclear. Here, we performed an exploratory whole-brain analysis focusing on hazard appearance, defined as the moment when a hazard first became visually available during an in-scanner driving simulator task. Forty-five participants (22-78 years) completed two tasks. Peripheral perceptual response time was measured using an orientation judgment task in the far periphery (>60 deg). Simulator-based hazard detection was measured as the latency from hazard appearance to first gaze to the hazard. At the first level, hazard appearance was modeled as an event. At the second level, the compensatory index was entered as a regressor of interest, with age and sex as covariates. Exploratory whole-brain analysis revealed positive associations between the compensatory index and activity in left insula, left middle temporal gyrus, and left superior temporal gyrus ($p<.001$ uncorrected, cluster extent $k>10$ voxels). The left middle/superior temporal findings may reflect early encoding of hazard appearance as a contextually meaningful dynamic event, potentially around the mid-to-posterior superior temporal sulcus, rather than as a mere visual change. Left insula activity may reflect the assignment of behavioral salience to the appearing hazard, marking it as relevant for action before overt gaze is directed toward it. Together with our previous mPFC/IFJ findings, these exploratory results point to candidate mechanisms by which drivers with relatively slow peripheral perceptual responses may nevertheless achieve efficient hazard detection: dynamic event processing and salience assignment at hazard appearance may precede subsequent context-based risk interpretation and attentional control supporting gaze allocation.

Disclosures: S. Murakami: A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **M. Cho:** A. Employment/Salary (full or part-time):; Honda R&D Co., Ltd. **D. Matsuyoshi:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **Y. Yomogida:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **R. Kanai:** A. Employment/Salary (full or part-time):; ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd.. **Y. Aizawa:** None. **M. Yamada:** 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.; Honda R&D Co., Ltd..

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.05/KK40

Topic: I.01. Attention

Support: NIH Grant MH135266

Title: Neural Mechanisms of Attention and Speech Processing in the Wild: EEG research goes to School

Authors: *E. ZION GOLUMBIC;
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Abstract: Understanding how attention operates in dynamic and noisy real-life environments, is a core translational challenge of cognitive neuroscience. Laboratory studies, while valuable for isolating specific mechanisms, often fail to capture the full complexity of real-world settings. To bridge this gap, instead of bringing participants to the lab, here we brought a mobile-lab to a real-life environment where attention is especially challenging: a typical high-school classroom.
We recorded neural activity (EEG), gaze and body motions from N=100 students, who viewed educational videos in their organic classroom, interspersed with occasional ecological disturbances. First, we verified that reliable neural speech-tracking responses could be obtained in this real-life mobile-EEG setting, and compared results to a parallel lab-based study using identical material. Next, we tested how learning-outcomes, neural speech tracking, gaze and posture were affected by the presence of background speech disturbances, and characterized the neural response to the disturbances themselves. We found that performance and neural speech tracking were negatively affected by background speech, however analysis of gaze and posture suggest investment of effort to maintain attention to the lecture despite the disturbances. We also found significant effects of time-on-task, with all measures associated with attention and speech processing deteriorating over the course of the lesson. Exploratory analysis further reveal interesting individual differences in both the effect the disturbances have on speech processing and the trajectory of changes over time.
This work emphasizes the feasibility and significance of conducting field-based neuroscientific research. Results from this real-world study challenge some long-held assumptions about how attention operates, based on traditional lab-based studies, and demonstrate the importance of including brain-body-behavior interactions when developing new models of real-life attention.

Disclosures: E. Zion Golumbic: None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.06/KK41

Topic: I.01. Attention

Support: NIH R01MH121099
NIH R01MH124115
NIH R01DA048096

Title: Time course of attentional capture and cognitive control in Parkinson's Disease

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Abstract: The progression of Parkinson's Disease (PD) is marked by debilitating motor symptoms and a loss of cognitive control that is associated with reduced quality-of-life measures. Dopamine-replacement medications aim to alleviate motor deficits but can have significant cognitive effects, exemplified by iatrogenic impulsive compulsive behaviors that occur in up to 20% of PD patients. We do not know exactly how PD or related medications affect cognitive control separately from their hallmark effects on motor functions. Prior investigations into cognitive control in PD show mixed results, potentially due to two limitations: 1) classical decision-making tasks conflate motor and perceptual processing, which simultaneously contribute to motor metrics like reaction times as well as to cognitive measures like choice accuracy, rendering them inseparable; and 2) inclusion of late-stage PD patients may eclipse finer differences in cognitive and motor control due to the extent of cellular degeneration.To study motor and cognitive changes in PD, we use an "urgent" version of the Eriksen flanker task. Urgent-choice paradigms yield a behavioral metric that reveals perceptual performance with millisecond temporal resolution. We exploit this technique to uncover differences in cognitive and motor control domains that are caused by PD, and to observe the impacts of medications on each domain. We recruited early-stage PD patients (Hoehn and Yahr Stages 1-2) to complete the urgent flanker task on one "ON" medication and one "OFF" medication session; the latter requires an 8-12 hour withholding of PD-related prescriptions. We recruited a cohort of participants without any primary neurological diagnoses as healthy controls to complete two sessions of the same task. The data shows time-locked attentional capture when the flanker stimuli are presented 120ms before targets, showcasing a temporal window when the exogenous pull of the distractors overwhelms endogenous cognitive control. Compared to healthy controls, PD patients show differences in the magnitude of attentional capture, and in the temporal dynamics of recovery from said capture, that vary with age, disease profile, and medication status. This work helps establish urgent choice tasks as a sensitive assay to differentiate the motor and cognitive deficits in Parkinsonian settings. We compute the time-cost of dopaminergic degeneration on attentional control and the changes associated with the onboarding of antiparkinsonian medications. These quantifications are of clinical and scientific interest, both for the development of better therapeutics and as a window into dopaminergic circuit function.

Disclosures: B.I. Sheikh: None. **A. Jiang:** None. **D. Shah-Zamora:** None. **E. Salinas:** None. **K.T. Kishida:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.07/KK42

Topic: I.01. Attention

Title: Nadamay Meditation Enhances P300 Event-Related Potentials and Sustained Attentional Processing

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Abstract: Nadamay Meditation Enhances P300 Event-Related Potentials and Sustained Attentional ProcessingAbstractBackground: Nadamay Meditation, a sound-based contemplative practice rooted in the Nada Yoga tradition,is theorized to cultivate increasingly refined attentional states through sustained engagement with auditoryexperience. Although meditation has been associated with improvements in attentional functioning, theeffects of Nadamay Meditation on event-related neural markers of attentional allocation and stimulusevaluation remain unknown. This study examined whether eight weeks of Nadamay Meditation alters P300event-related potentials during auditory oddball processing.Methods: A total of 82 healthy adults were enrolled in a single-blind, three-arm randomized controlled trialand randomized to Nadamay Meditation, Indian classical music listening, or mind-wandering controlconditions. EEG was recorded during an auditory oddball paradigm at baseline and after eight weeks.Primary outcomes included frontal P300 amplitude, latency, and area under the curve (AUC), a measurereflecting sustained post-stimulus neural activity.Results: Participants in the Nadamay Meditation group demonstrated significant enhancement of frontalP300 amplitude following training (within-group dz = 0.68), with large between-group effects relative toboth control conditions (Cohen's d up to 1.31). Meditation training also produced marked increases in P300AUC, indicating greater sustained attentional neural engagement. At electrode F3, AUC increased by 228.7μV·ms, while participants in the mind-wandering condition exhibited significant reductions over time.Between-group differences were large (d = 1.09 versus Mind-Wandering). Changes in P300 latency werecomparatively modest. Active and passive control groups showed limited evidence of comparable neuralenhancement.Conclusions: These findings provide the first evidence that Nadamay Meditation selectively strengthensneural signatures of attentional allocation and sustained information processing. Enhanced P300 amplitudeand AUC suggest improved efficiency of attentional engagement and conscious stimulus evaluationfollowing sound-based contemplative training. P300-derived measures may serve as sensitive biomarkersof meditation-related neuroplasticity and attentional optimization.Keywords: Nadamay Meditation, P300, event-related potentials, auditory oddball, attention, EEG,meditation, neuroplasticity

Disclosures: K. Megha: None. **S. Patra:** None. **G. Kumar:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.08/KK43

Topic: I.01. Attention

Support: R01HD105735

Title: The utility of Free Visual Exploration for spatial neglect detection in chronic right hemisphere stroke

Authors: *K. STACK, A. SEYDELL-GREENWALD;
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Abstract: Unilateral spatial neglect (SN), the inability to attend or respond to stimuli in the contralesional hemispace in the absence of broad sensorimotor impairment, is common after right hemisphere (RH) stroke. Up to 1/3 of patients with acute neglect continue to have neglect in the chronic phase. Paper and pencil assessments (e.g., cancellation, line bisection, figure/shape copying) continue to be widely used diagnostics of SN after stroke, but can have poor sensitivity to mild neglect and show strong practice effects. Recently, free visual exploration (FVE) of scenes has been proposed as a fast and cognitively undemanding assessment of SN that is a better classifier of leftward SN than paper-pencil tests in sub-acute RH stroke patients with neglect in everyday behavior. The present analysis investigates the utility of FVE in the assessment of SN in chronic RH stroke. Thirty RH stroke survivors (>1 year post-stroke; mean age 57.3; 13 female) and 14 neurologically healthy adults (mean age 57.9; 9 female) completed a FVE task during which gaze position data was collected by a stationary eye tracker. Four RH stroke survivors were determined to have current gross unilateral SN, as classified by markedly impaired performance on both visual perception and standard paper pencil assessments. The remaining RH stroke survivors were classified as “without SN” but did show residual attentional biases compared to controls as evidenced by a significant group difference in proportional left/right reaction times on a visual search task (p = .008). One-way ANOVAs with Fisher's Least Significant Difference correction showed RH stroke survivors with SN had significantly more rightward initial and mean gaze fixation positions than controls and RH stroke survivors without SN, and also had significantly lower of proportions of left-sided initial and overall fixations (all p <= .015). There were no significant differences in any of the gaze metrics between RH stroke survivors without SN and controls. Additionally, fixation metrics were significantly correlated with the proportional left/right reaction time difference during visual search for the SN group only. These findings suggest that in the chronic phase of stroke, gaze position metrics can still identify RH stroke survivors with severe neglect. However, they do not reveal sub-clinical lateralized attentional biases in RH stroke survivors without gross neglect. FVE remains a promising tool for SN assessment, but longitudinal research to evaluate changes in gaze position metrics during recovery of neglect and additional investigation in chronic neglect patients, is still needed.

Disclosures: K. Stack: None. **A. Seydell-Greenwald:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.09/KK44

Topic: I.01. Attention

Support: NIA Grant R01AG088329-01

Title: Modulation of Stimulus-driven Visual Processing by Prestimulus Alpha Power: Indications of Age-Related Decoupling

Authors: *M. KANG[1], K. KRASICH[2], K. ROBERTS[1], A. HOWARD[1], H. SANCHEZ MELENDEZ[1], M. G. WOLDORFF[1], L. ACKER[1];
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Abstract: The neural response to a visual stimulus unfolds across different processing stages, including sensory gain and salience detection processes, which are reflected electrophysiologically in early posterior negativity (e.g., N1, latency 150-250 ms) and early frontal positivity (latency 170-250 ms) event-related potential (ERP) components. Prestimulus posterior cortical states modulate these stimulus-elicited processes. In particular, lower posterior prestimulus EEG alpha power (8-12 Hz), which generally reflects higher cortical excitability, has been associated with greater stimulus-elicited early posterior negativity ERP responses, reflecting coupling between prestimulus cortical excitability and subsequent sensory gain mechanisms. Aging is associated with reduced neural network integrity, which may weaken or alter this coupling, although little research has investigated such a possible effect. The present study investigated how prestimulus cortical excitability, indexed by alpha power, modulates stimulus-driven visual processing—as indexed by early posterior negativity and frontal positivity ERP effects—in younger and older adults. We recorded an electroencephalogram (EEG) from younger (n=31; mean age 20) and older (n=56; mean age 71) adults during a visual Stroop task. We examined ERPs elicited by the Stroop stimuli as a function of within-subject prestimulus alpha power, divided into tertiles (low, medium, high). A cluster-based permutation approach tested differences between low and high prestimulus alpha conditions across electrodes within 150-250 ms post-stimulus, allowing assessment of posterior and frontal ERP modulations as a function of prestimulus alpha (high versus low) in each group. In younger adults, both posterior negative and frontal positive clusters were observed, with greater posterior negativity and frontal positivity following low versus high prestimulus alpha power. In striking contrast, in older adults, only a frontal positive cluster emerged, indicating greater positivity following low versus high alpha, with no posterior negativity effect. Qualitatively, the frontal positivity cluster appeared to occur later in older adults (~200 ms) than in younger adults (~150 ms). These findings provide electrophysiological evidence of age-related alterations in the coupling between prestimulus visual cortical excitability and stimulus-driven visual processing, consistent with

reduced neural integrity in aging. Future studies will examine the clinical implications of this decoupling and test whether modulating cortical excitability can restore this coupling in older adults.

Disclosures: M. Kang: None. **K. Krasich:** None. **K. Roberts:** None. **A. Howard:** None. **H. Sanchez Melendez:** None. **M.G. Woldorff:** None. **L. Acker:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.10/KK45

Topic: I.01. Attention

Support: NIH Grant R01HD105735

Title: Utility of the Cookie Theft Picture for detecting chronic hemispatial neglect after right hemisphere stroke

Authors: *H. ANDERSON, K. STACK, A. SEYDELL-GREENWALD;
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Abstract: Analysis of verbal picture description is a valuable component of post-stroke assessment. Previous studies have compared narrative output across various populations, such as left hemisphere (LH) and right hemisphere (RH) stroke survivors and neurologically healthy controls. The Cookie Theft picture from the NIH Stroke Scale (NIHSS) is a prevalent measure that captures differences between groups by integrating open-ended visual scanning and language generation. Recent studies highlight aspects of picture description that are distinctive for RH stroke survivors, including lowered ratio of left:right content units (LRCU). This difference has been attributed to left hemispatial neglect (SN) which is common in RH stroke survivors and could cause them to describe fewer concepts on the left side of the picture. However, a direct link between SN and a lowered LRCU ratio within a RH stroke group has yet to be shown. Moreover, it is unknown whether a lowered LRCU ratio will still be observed in the chronic phase of stroke, when neglect symptoms are generally milder and less prevalent. To address these gaps, we selected, from a larger group of chronic RH stroke survivors participating in a study of visuospatial impairments after stroke, a subset with clear evidence of persistent SN (mean age 67.8; 3 White, 2 Black; 3 male, 2 female) according to a large battery of neglect measures (including visual perception and classic paper-pencil tasks), and a demographically matched group of chronic RH stroke survivors without SN (mean age 64.6; 3 White, 2 Black; 3 male, 2 female). For all participants, we scored the NIHSS Cookie Theft picture description for LRCU and ran an independent samples t-test to analyze for significant differences between groups. The group with SN had a LRCU ratio of 0.77 (SD 0.47), and the LRCU ratio of the group without neglect was 1.05 (SD 0.28). While the group difference did not reach significance, likely due to the small sample size, it did go in the expected direction. Moreover, the LRCU of

the neglect group was comparable to that observed in a prior study of acute stroke patients with neglect, and at 1.05, the LRCU observed in the non-neglect group fell between that observed in acute neglect patients (0.78) and neurologically healthy controls (1.19) in that same study. These findings suggest that the NIHSS Cookie Theft picture description may have clinical utility for capturing evidence of SN even in chronic stroke, which is particularly relevant given the test's accessibility and ease of administration. Future studies should expand upon these findings by analyzing larger sample sizes to improve confidence and further clinical applicability.

Disclosures: H. Anderson: None. **K. Stack:** None. **A. Seydell-Greenwald:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.11/KK46

Topic: I.01. Attention

Support: Secretaría de Ciencia Humanidades, Tecnología e Innovación (SECIHTI) (EAM-931445)
SIREI (TCLL-43200202477)
Sistema Nacional de Investigadoras e Investigadores (SNI) (TCLL-210785)

Title: Disordered eating behaviors in adults with and without ADHD: preliminary findings

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Abstract: Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by symptoms of inattention, hyperactivity, and impulsivity. Emerging evidence suggests that these symptoms may contribute to disordered eating behaviors through alterations in self-regulation and reward-related processes. This preliminary study examined differences in disordered eating behaviors between adults with and without ADHD.**Objective:** To examine differences in disordered eating behaviors between adults with and without Attention-Deficit/Hyperactivity Disorder (ADHD).**Methods:** A preliminary findings study was conducted in Mexico with adults aged 18 to 40 years. Participants were divided into two groups: individuals with a psychiatrist-confirmed diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD; n = 5) recruited from a psychological clinic, and community controls without an ADHD diagnosis (n = 10) recruited from the general population. Participants completed the Adult ADHD Self-Report Scale (ASRS v1.1), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI-II), and the Brief Questionnaire of Risky Eating Behaviors (CBCAR). Descriptive statistics were calculated for all

variables, and group differences were examined using the Mann-Whitney U test, with statistical significance set at $p < .05$.**Results:** Anxiety, depression, ADHD symptomatology, and disordered eating behaviors were compared between adults with an ADHD diagnosis ($n = 5$) and individuals from the general population ($n = 10$) using the Mann-Whitney U test. Participants with ADHD showed significantly higher scores on disordered eating behaviors ($U = 8.0$, $p = .042$). Additionally, a trend toward higher ADHD symptomatology was observed in the ADHD group ($U = 10.5$, $p = .086$). No significant differences were found in anxiety or depression scores. Effect size analyses revealed large effects for both ADHD symptoms (ASRS; $d = 1.02$) and disordered eating behaviors (CBCAR; $d = 1.46$).**Conclusions:** Preliminary findings suggest that adults with ADHD exhibit higher levels of disordered eating behaviors compared to individuals from the general population. Although the sample size was small, the results support the need for further research examining the relationship between ADHD and disordered eating behaviors in adults.

Disclosures: A. Rodríguez Montero: None. **T. Cibrian-Llanderal:** None. **R.L. Castillo López:** None. **S. Valencia:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.12/KK47

Topic: I.01. Attention

Support: BIAL Foundation Research Grant 92/18

Title: Mind the Lag: Trait Non-Reactivity and Equanimity Attenuate Emotional Attentional Blink in Meditators

Authors: *A. HAMID SAIFULLAH[1], R. PANDEY[2], L. ALDRIDGE-WADDON[3], V. TRIPATHI[4], V. KUMARI[5], E. ANTONOVA[6];
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Abstract: The human attentional system can handle a stream of incoming sensory stimuli, yet has limited resources. The temporal limitations of an attentional system can be studied using the *Attentional Blink* (*AB*) phenomenon, signifying a reduced ability to detect a second target stimulus (T2) when preceded by a first target stimulus (T1) within 200ms-500ms. Mindfulness meditation attenuates *neutral attentional blink (NAB)* and *emotional attentional blink (EAB)* by increasing capacity of an otherwise limited attentional system and reducing *attentional capture* by emotional stimuli. *NAB* and *EAB* paradigm performance and its association with trait mindfulness (*non-reactivity*) and *equanimity* (non-attachment towards present-moment

experiences) were investigated in 129 participants, including 75 meditators (Male/Female: 47/28) and 54 non-meditators (Male/Female: 37/17), with T1-T2 intervals (lags) varying between 200ms-700ms. For the *EAB* paradigm at lag 200ms, female meditators had significantly higher response accuracy for both T1 and T2 stimuli when T1 stimuli was *emotional* rather than *neutral*; this effect was not observed in male meditators or for either sex in non-meditators. In mindfulness meditators, both higher trait *non-reactivity* and *equanimity* were associated with smaller *EAB* at lag 300ms when T1 was *emotional.* This is the first study to show an association between smaller *EAB* and higher trait *equanimity* in mindfulness meditators, highlighting the effect of mindfulness practice on emotional regulation. Findings also suggest the differential effects of meditation on emotional processing in females as indexed by *EAB* paradigm performance.

Disclosures: A. Hamid Saifullah: None. **L. Aldridge-Waddon:** None. **V. Kumari:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.13/KK48

Topic: I.01. Attention

Title: Ultra-Mobile EEG Field Recordings Reveal Altitude-Dependent Changes in Cortical Processing

Authors: *C. GUGER[1], S. SIEGHARTSLEITNER[1,2], R. HOFMEISTER[1], K. MAYR[1], J. GRUENWALD[1];
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Abstract: High-altitude hypoxia can impair cognitive performance and cortical processing, yet electrophysiological measurements under real expedition conditions remain technically challenging because of constraints on mobility, power supply, environmental robustness, and stimulus timing precision. We present an ultra-mobile EEG field workflow for recording evoked and resting-state brain activity during an expedition to Mount Kazbek (Georgia, 5054 m). EEG data were acquired at five altitudes, from approximately 300 m to 4200 m, including repeated measurements after ascent/descent cycles and post-expedition recovery. The experiment was implemented in g.Pype, a Python-based framework for real-time stimulus presentation, EEG acquisition, signal processing, and visualization. The complete paradigm and processing workflow were deployed via g.Pype Runtime as a standalone executable, enabling tablet-based, battery-powered operation without a conventional laboratory setup. This allowed precise visual stimulation, synchronized wireless EEG acquisition using a BCI Core-8, and immediate quality control in an ultra-mobile environment, including field conditions with temperatures down to approximately -20°C and limited access to charging infrastructure. Visual evoked/event-related responses showed pronounced altitude-dependent modulation. At approximately 300 m, response

amplitudes were about 10 μV with short latencies. At 1700 m, amplitudes decreased to approximately 4 μV and latencies increased; at 3000 m, amplitudes remained reduced at approximately 3.5 μV, with the longest observed latencies. After ascending to 4200 m and returning to 3700 m, amplitudes increased again to approximately 5.5 μV and latencies shortened toward baseline, consistent with acclimatization. After the expedition, amplitudes increased to approximately 12 μV and latencies returned to short values, suggesting recovery or possible rebound effects following altitude exposure. Resting-state EEG also changed with altitude: relative alpha power increased slightly from 0.17 at 300 m to 0.185 at 1700 m, but decreased to 0.145 at 3000 m and 0.125 at 3700 m after exposure to 4200 m. Together, these findings indicate reduced cortical response strength, delayed information processing, altered resting-state dynamics, and acclimatization-related changes during high-altitude exposure. The study demonstrates that precise EEG-based assessment of cortical function is feasible in extreme mobile environments and that deployable real-time software workflows can extend neurophysiological research beyond conventional laboratory settings.

Disclosures: 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. **S. Sieghartsleitner:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **R. Hofmeister:** 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. **J. Gruenwald:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.14/KK49

Topic: I.01. Attention

Support: Plutonium IDUB grant

Title: Frontotemporal spectral power induced by volitional attentional modulation is dysregulated in ADHD: a dual EEG and BCI study

Authors: B. M. NAPARLO[1], Z. NASIRI[2], L. KOZICKA[2], D. RYTUS[2], J. LASZYCA[2], S. PYSKOWACKI[2], A. MARCINKOWSKA[1], J. S. GARCIA SALINAS[2], *M. T. KUCEWICZ[3]; [1]Dept. of Neurophysiology, Neuropsychology and Neuroinformatics, Med. Univ. of Gdansk, Gdansk, Poland; [2]Fac. of Electronics, Telecommunications and Informatics, [3]Gdansk Univ. of Technol., Gdansk, Poland

Abstract: Due to a rising prevalence of attention-deficit/hyperactivity disorder (ADHD) diagnoses (NIMH, 2023) and evidence that neurofeedback interventions may reduce ADHD symptoms (Wu et al., 2024), a study combining neuropsychological assessment,

electroencephalography (EEG), and a single-channel brain-computer interface (BCI) technology was conducted. Frontal theta/beta ratio (TBR) is a well-established EEG marker of executive attention, elevated in ADHD and negatively correlated with attentional control in neurotypical adults (Angelidis et al., 2016; Wang et al., 2024). Event-related theta, alpha, and beta power in prefrontal and frontal cortical regions reliably distinguish attentional states (Lim et al., 2019), and meta-analytic data confirm consistent spectral power alterations across these bands in ADHD (Michelini et al., 2022). We recruited 33 adults (13 formally diagnosed ADHD, 20 neurotypical controls; mean age 22.7 ± 3.2 years; 69% female; mean education 15.5 ± 2.3 years). Participants completed neuropsychological tests (Stroop/D-KEFS, d2-R, Corsi Block Tapping Test) and then performed a BCI task during simultaneous 32-channel EEG recording. Each subject lifted a physical ball for five seconds using sustained mental focus (UP) and then lowered it (DOWN) by disengaging attention, creating a within-subject UP versus DOWN task-state contrast. Spectral features were extracted in overlapping windows across a ±3-second epoch around each UP/DOWN event marker. We found significant group effects (ADHD vs non-ADHD) at consistent frontotemporal sites with the gamma, alpha, alpha/beta, and theta spectral features. Significant Group × Event interactions were observed around the event transition point and in the post-transition windows for the theta-, alpha-, beta-, and gamma-band spectral features over specific frontal and frontotemporal electrode sites. These effects suggest that the ADHD vs non-ADHD group differences in event-related volitional modulation of EEG activities were induced by maintaining attention through the UP/DOWN task-state transition rather than by reaching its maximal level. These task-induced differences were specific to the frontal and frontotemporal electrode sites and were not evident in the resting state condition. Our results are congruent with the previously reported frontotemporal areas and spectral activities, suggesting potential biomarkers of attention state transitions in specific frequency bands and anatomical sites as targets for the emerging neurofeedback therapy designs for ADHD.

Disclosures: B.M. Naparlo: None. **Z. Nasiri:** None. **L. Kozicka:** None. **D. Rytus:** None. **J. Laszyca:** None. **S. Pyskowacki:** None. **A. Marcinkowska:** None. **J.S. Garcia Salinas:** None. **M.T. Kucewicz:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.15/KK50

Topic: I.01. Attention

Title: Longitudinal Effects of Mantra-Based Meditation on Functional Connectivity

Authors: G. OZBEKOGLU[1], A. LI[2], B. H. COHEN[3], ***S. AVIYENTE**[1], S. RAVISHANKAR[1]; [2]Computat. Mathematics, Sci. and Engin., [1]Michigan State Univ., East Lansing, MI; [3]Applied Psychology, New York Univ., Greenwich, CT

Abstract: Recent studies on contemplative practices have demonstrated that meditation induces profound psychological and physiological changes, most commonly increased theta and alpha power. However, complex brain activity during meditation may not be adequately described by basic electroencephalography (EEG) power spectral analyses, which provide no information about the organization of interactions between brain regions. More advanced measures such as functional connectivity, i.e. how efficiently information is exchanged across the whole network, are needed to assess the modulation of network-level dynamics. While meditation training is associated with changes in large-scale brain networks, it remains unclear whether different mantra practices produce distinct functional connectivity patterns. In this study, we investigated fronto-parietal functional connectivity using EEG from 31 participants who completed a six-week meditation training intervention: 16 Hare Krishna (HK) and 15 Sa-Ta-Na-Ma (SA) practitioners. Subjects were randomly assigned to either group before initial training and practiced Japa meditation (both audible and silent or inner speech repetition of the mantra with focus) daily, increasing from 5 min/day in week 1 to 10 min/day in week 2 and 15 min/day thereafter; compliance was monitored via online journaling. EEG was recorded before and after training and involved a sequence of eyes-closed resting-state and vocalized or silent meditation conditions. Functional connectivity was quantified using the phase-locking value (PLV) derived from the Reduced Interference Distribution (RID)-Rihaczek time-frequency representation for the fronto-parietal subnetwork in the alpha band. Training-related connectivity changes were evaluated using edge-wise Wilcoxon signed-rank tests. Comparing silent meditation after versus before training, the two mantra practices showed opposing patterns of fronto-parietal alpha-band connectivity. Following training, HK practitioners showed maintained-to-increased phase synchronization in the fronto-parietal region, a pattern compatible with strengthened top-down engagement of the fronto-parietal control network during mantra repetition. SA practitioners showed reduced coupling concentrated in frontal and fronto-parietal connections, alongside preserved posterior synchronization, consistent with diminished cognitive-control demand and greater automaticity or internal absorption. If confirmed, the two practices may train distinct attentional regimes—active top-down control versus automatized absorption—rather than a common mechanism of differing strength.

Disclosures: G. Ozbekoglu: None. **A. Li:** None. **B.H. Cohen:** None. **S. Aviyente:** None. **S. Ravishankar:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.16/KK51

Topic: I.01. Attention

Support: Masters of Arts in Psychological Science, UMD

Title: The P3 auditory evoked potential habituates at the same rate and to the same degree in adults with ADHD when on and off their ADHD medication as in controls

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Abstract: Wehypothesized that ADHD is due to hyper-habituation. We examined this premisewith a paradigm which did not involve an emotional/ANS or motor/rewardresponse. Thirty adult (*M* = 23yo) participants diagnosed with ADHD, whowithheld their ADHD medication prior to one of two assessments, and 31 adultcontrol participants (*M* = 20yo) were compared. As expected, the indexsample (*M* = 18.03, *SE* = 0.886) and control sample (*M* =7.26, *SE* = 0.89) differed significantly and meaningfully on the SheehanDisability Scale (*t* = 8.66, *p* < .001, Cohen's *d* = 4.9).At rest, participants listened to a sequence of 300 tones (119 Hz, 70 dB, 100ms) at intervals of 1.25 seconds with EEG recorded (area Cz). Six successiveblocks of 50 trials were averaged per individual, and the amplitude of amid-latency wave measured (positive peak at 450 ms post stimulus onset). A 2x6mixed ANOVA found a significant reduction in amplitude across the 6 blocks oftones, but no difference in the two groups, and no group by block interaction.When unmedicated ADHD participants were compared to presently medicated ADHDparticipants, again no differences could be found in either amplitude orattenuation in amplitude across the 6 blocks of stimuli. We interpret the nullfindings regarding AEP amplitude as not resulting from insufficient statisticalpower/sample sizes. The present paradigm was highly sensitive to differencesacross the blocks of recordings (*p* = .001, η^2 = .266). At thesame time, differences between groups were barely measurable (group η^2 =.014). For each of the six blocks, assessed separately, the strength of therelationship between groups ranged from an η^2 of .003 to .018. Indeed,there was no Block by Group interaction, with an η^2 equaling zero.Nevertheless, these sample sizes were sufficient to easily discriminate betweencontrols and ADHD participants on and off their ADHD medication using theSheehan Disability Scale. These results suggest the two groups were stronglyand sufficiently different in their symptomology to reflect a difference in AEPcharacteristics if one existed. Other studies involving rewarding tasks orrequiring a behavioral response or assessing autonomic/emotional responsesreport greater habituation in participants with ADHD. These findings, whichdiverge from the present study, suggest that the neurological locus responsiblefor ADHD is at a later stage of processing, beyond sensory gating (at least inadults). The lack of differences between ADHD participants on and off theirADHD medications suggest that the therapeutic effects of these compounds alsotake place at a level beyond sensory gating.

Disclosures: A. McCarty: None. **R.L. Lloyd:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.17/KK52

Topic: I.01. Attention

Support: SECIHTI fellowship 1311691
PAPIME Project PE202626

Title: Digital media use and cognition of Medical Students: Attention, Intelligence, and Academic Performance

Authors: *A. A. HERNANDEZ CHAVEZ[1,2], J. STAUFERT[3], A. BARAJAS-MARTÍNEZ[4], J. URIARTE-ORTIZ[3], A. MUNOZ-COMONFORT[3], R. SAMPIERI[3];
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Abstract: Introduction: Electronic media are central to university life, yet excessive screen exposure may interfere with attention, working memory, and adaptive reasoning. This study explored how digital screen time and related behaviors are associated with different dimensions of intelligence (fluid and crystallized), attention, and academic performance in second-year medical students. Methods: An observational, cross-sectional study was conducted in 305 second-year medical students from a public university in Mexico. Screen exposure was measured with a validated Screen Time Survey. Intelligence was assessed with the Shipley-2 test, including crystallized intelligence (Gc), fluid intelligence (Gf), general cognition, and cognitive impairment indices. Academic performance was obtained from standardized physiology examinations and official academic records. In a randomly selected subsample (n = 30), EEG was recorded during a P300 oddball paradigm; N100, N200, P300 latency, and P300 amplitude were analyzed as attentional markers. Weighted network analysis was performed with igraph in R among 34 cognitive, behavioral, socio-academic, and academic variables. Results: Students reported 7.1 ± 4.3 h/day of screen exposure. Higher screen time was associated with lower academic performance ($r = -0.24$, $p < 0.001$). Cognitive impairment was associated with Gf ($R^2 = 0.848$) and general cognition ($R^2 = 0.400$), but not with Gc ($R^2 = 0.001$). ERP measures showed mean latencies of 86.7 ± 24.6 ms for N100, 191.1 ± 31.9 ms for N200, and 358.33 ± 45.6 ms for P300, with P300 amplitude of 259.63 ± 61.6 μV. Shorter N100 latency correlated with better academic performance ($r = -0.45$, $R^2 = 0.199$). Network analysis revealed a modular structure linking digital media use, intelligence, socio-academic factors, and academic outcomes. Total screen time, failed courses, age, and physiology performance were central nodes, while texting, social media, and short-form video use acted as bridges. Discussion and conclusion: Excessive digital media exposure was associated with lower academic performance, reduced cognitive efficiency, altered attentional processing, and changes in cognitive-academic network organization. Although causal inference cannot be established, this multimodal approach provides convergent evidence that digital environments may shape attention-dependent learning and support interventions to promote healthier habits and cognitive well-being.

Disclosures: A.A. Hernandez Chavez: None. **J. Staufert:** None. **A. Barajas-Martínez:** None. **J. Uriarte-Ortiz:** None. **A. Munoz-Comonfort:** None. **R. Sampieri:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.18/KK53

Topic: I.01. Attention

Title: Long-Lasting Effects of Psychedelics on Neural Connectivity Associated with Goal-Directed Behavior in Humans

Authors: A. NELSON, D. CHANG, ***A. NAVARRO-CEBRIAN**;
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Abstract: Research into psychedelic drugs over the past 20 years have focused on their long-lasting curative effects regarding resistant psychiatric disorders ranging from major depressive disorder to obsessive compulsive disorder. Many findings have shown changes in functional connectivity within the Default Mode Network (DMN), but few studies have looked at the connectivity in areas anti-correlated with the DMN like the salience (SN) or central executive network (CEN). Communication between these two networks (SN and CEN) lies at the core of how the brain transforms goals into controlled actions. We looked at the connectivity of the SN, specifically the left and right dorsal anterior cingulate cortex (l-dACC; r-dACC). We utilized the data collected by Egger et al. This team administered 120 mg of either placebo or N,N-dimethyltryptamine (DMT) randomly to 40 meditation practitioners at a 3-day meditation retreat. Functional magnetic resonance imaging (fMRI) scans were taken 48 hours before and after treatment administration. We computed functional connectivity of the l-dACC and r-dACC using a predefined parcellation. For each subject, connectivity matrices were estimated at pre- and post-treatment, and change scores (Δ = post - pre) were calculated. Then, we identified group (drug vs. placebo) differences using a mixed-effect model with factors group, hemisphere, and ROI. Main effects ($F(1,152) = 22.32$; $p < 0.001$) show that DMT significantly altered connectivity. Specifically, 48 hours after treatment, l-dACC and r-dACC were significantly more correlated with both left and right dorsolateral prefrontal cortex (CEN) in subjects who took DMT compared to the placebo. Our results indicate that these changes are not limited to the acute effects of the drug but persist for at least 48 hours after administration.

Disclosures: A. Nelson: None. **D. Chang:** None. **A. Navarro-Cebrian:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.19/KK54

Topic: I.01. Attention

Title: Bidirectional Modulations of Individual Alpha Dynamics Across Different Mantra-Based Meditation Techniques

Authors: ***A. LI**[1], J. RODRIGUEZ-LARIOS[4], M. ZHANG[1], T. LIU[2], B. H. COHEN[5], S. RAVISHANKAR[1,3];
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Abstract: Mantra-based meditation techniques tend to be lumped under "Focused Attention", despite potential variations in neural states that may be induced by different mantras or instructions. To address this lack of nuance, we conducted a six-week electroencephalography (EEG) study in which 58 novice subjects were randomly assigned to practice Japa meditation with one of two structurally distinct mantras. The Hare Krishna (HK, n=31) group repeated a 16-word rhythmic sequence, while the Sa-Ta-Na-Ma (SA, n=27) group repeated a simple four-syllable cycle. High-resolution 64-channel EEG was recorded pre- and post-intervention using a sequence of eyes-closed tasks, including pre-task rest, vocal chanting, post-chanting rest, and silent (mental) repetition. Utilizing spectral parameterization (FOOOF) to separate periodic oscillations from the aperiodic (1/f) background, we tracked modulations in individual alpha power (IAP), individual alpha frequency (IAF), and the alpha band center of gravity (CoG). The two practices revealed marked, opposing differences in alpha dynamics. In the resting state following overt chanting, the HK group exhibited a frequency acceleration in both IAF and CoG relative to pre-task rest. Subsequently, during the silent meditation task, the HK group demonstrated a state of heightened cortical activation, characterized by topographically widespread IAP reduction alongside sustained elevations in IAF and CoG relative to resting. This active neural profile became even more pronounced after six weeks of daily practice. In contrast, the SA technique induced minimal initial frequency alterations, showing only a localized, left-frontal IAP reduction during early meditation practice. Crucially, after six weeks of practice, the SA group demonstrated a frontal-central reduction of both IAF and CoG during post-chanting rest and during silent meditation compared to pre-intervention baselines. While psychological data confirmed that both groups achieved significant and comparable reductions on the Perceived Stress Scale (PSS), their underlying neural trajectories fundamentally diverged. This demonstrates that the structure of a mantra is a critical variable driving distinct neurophysiological states. We hypothesize that HK functions as a high-load cognitive task that upregulates arousal and enhances focused attention, whereas the lower working memory load of SA promotes cortical inhibition and deep relaxation. This study challenges the monolithic classification of mantra-based practices and highlights the need for precise, mechanism-driven behavioral prescriptions in clinical and contemplative contexts.

Disclosures: A. Li: None. **J. Rodriguez-Larios:** None. **M. Zhang:** None. **T. Liu:** None. **B.H. Cohen:** None. **S. Ravishankar:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.20/Web Only

Topic: I.01. Attention

Title: Persistent Homology Reveals Differences in Single-Trial Auditory EEG Topology Between Expert and Novice Mantra Meditators

Authors: *C. SRIVASTAVA[1], T. RATH[2], J. BEURIA[3], R. GUPTA[1];
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Abstract: Recent developments in network neuroscience have employed topological data analysis (TDA) to study features of neural data that may not be readily captured by conventional time series analysis. Applications of TDA to brain dynamics have been noted for their robustness to noise, and studies have documented persistent homology as an emerging tool for modeling individual differences in brain function. Building on this approach, we applied TDA to single-trial EEG responses elicited by standard (S80) and oddball auditory tones (D90/D70), collected from expert and novice mantra meditators (n=27 per group) during a passive auditory oddball paradigm designed to measure mismatch negativity. Participants passively listened to an auditory intensity oddball paradigm comprising 80 dB standards (80%) and 70 dB and 90 dB oddball deviants (10% each), presented with a jittered inter-stimulus interval (450-550 ms) across two 500-stimulus blocks. Single-trial EEG waveforms from the Fz and Cz electrodes were transformed into Takens delay-coordinate embeddings. Vietoris-Rips persistent homology was then computed for each embedded trajectory in dimensions H0 and H1. The resulting persistence diagrams were summarized using Betti curves, persistence entropy, and persistence-image-based features. After exploratory screening, we locked a restricted H0 entropy family and reran 20 tests with 10,000 permutations. Results indicated that experts exhibited higher mean H0 entropy than novices at Fz for D90 deviants ($d = 0.939$, $q = 0.000444$), D70 deviants ($d = 0.863$, $q = 0.00122$), and S80 standards ($d = 0.808$, $q = 0.0018$). In contrast, experts showed lower across-trial H0 entropy variability for D90 deviants ($d = -0.966$, $q = 0.000444$) and S80 standards ($d = -0.829$, $q = 0.000444$). Similar to Fz, Cz also showed directionally consistent effects for the locked H0 entropy features, although effect sizes were smaller than those observed at Fz, reinforcing the expert-novice difference. Higher H0 entropy can be interpreted as a more evenly distributed component-merging profile, while lower across-trial H0 entropy variability indicates greater trial-to-trial consistency. Therefore, these findings suggest that meditation expertise may be associated with more stable frontocentral auditory response geometry. More broadly, these results support persistent homology as a complementary framework for characterizing topological structure in neural response dynamics and its relationship to individual differences in cognitive function.

Disclosures: C. Srivastava: None. **T. Rath:** None. **J. Beuria:** None. **R. Gupta:** None.

Poster

PSTR245: Clinical and Applied Mechanisms of Attention in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR245.21/KK56

Topic: I.01. Attention

Support: R01HL171813
K25HL151912
R21HL165320

Title: Neural basis of improved sustained attention following sleep apnea treatment

Authors: *D. Z. AZAD[1], D. I. VALENCIA[1], V. BUILOFF[1], S. WICKRAMARATNE[1], K. KAM[1], L. FLEYSHER[2], A. W. VARGA[1], I. AYAPPA[1], D. M. RAPOPORT[1], A. PAREKH[1]; [1]Pulmonary, Critical Care & Sleep Med., Icahn Sch. of Med. at Mount Sinai, NEW YORK, NY; [2]BioMedical Engin. and Imaging Inst., New York, NY

Abstract: Obstructive sleep apnea (OSA) is associated with impaired sustained attention. Neural mechanisms by which continuous positive airway pressure (CPAP) may restore vigilance remain unclear. Since the thalamus supports arousal and attention regulation, we tested whether thalamic activation during a psychomotor vigilance task (PVT) differs by CPAP condition and attentional performance. Twenty-one adults with OSA who were adherent to AutoPAP (14 male/7 female; age=57±10 years; BMI=33±7 kg/m2) completed counterbalanced overnight polysomnography on-CPAP and off-CPAP. The following morning, participants performed a PVT during fMRI. Lapses were defined as reaction time ≥500ms, and participants were categorized as attentive or non-attentive using a median split (<7.1 vs. >7.1 lapses). Functional images were preprocessed in AFNI and analyzed using general linear models and group-level mixed-effects analyses focused on thalamic activity for on-CPAP versus off-CPAP and attentive versus non-attentive contrasts. Cluster threshold was set at ≥20 contiguous voxels. On-CPAP was associated with higher thalamic activation than off-CPAP in left (57 voxels; center of mass=-7.1, 19.7, 6.1; mean beta=0.145) and right (39 voxels; center of mass=10.8, 12.2, 5.3; mean beta=0.146) thalamic clusters. Attentive versus non-attentive analyses identified two left thalamic clusters (51 and 29 voxels; mean beta=-0.193 and -0.165), consistent with reduced thalamic activity in participants with higher lapses. PVT performance showed a trend toward fewer lapses on-CPAP and greater lapse burden in the non-attentive group. These preliminary findings suggest that CPAP-related improvements in sustained attention may involve greater thalamic recruitment during sustained attention. Thalamic activation may therefore provide a neural marker of variability in cognitive response to OSA treatment.

Disclosures: D.Z. Azad: None. **D.I. Valencia:** None. **V. Builoff:** None. **S. Wickramaratne:** None. **K. Kam:** None. **L. Fleysher:** None. **A.W. Varga:** None. **I. Ayappa:** None. **D.M. Rapoport:** None. **A. Parekh:** F. Consulting Fees (e.g., advisory boards); Yuimedi Corp.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.01/KK58

Topic: I.04. Executive Functions

Title: Investigating Arousal-Related Changes in Brain Network Functional Connectivity Using Traditional vs. Precision fMRI

Authors: *P. KIM[1], A. TRIANA[1], M. MITCHELL[2], G. WULFEKUHLE[3], D. C. PEREZ RIVERA[5], Z. LADWIG[6], A. JAIMES[4], A. DWORETSKY[7], J. HERNANDEZ[6], J. CHERNICKY[2], N. R. LABORA[4], C. GRATTON[2];
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Abstract: Low arousal reduces performance in attention, decision making, and reasoning tasks differently across individuals. Supported by coordinated activity across large-scale brain networks, functional connectivity (FC) is useful for examining how neural co-activation changes with arousal. While most fMRI research shows strengthened sensory/motor FC during low arousal, these studies primarily rely on group-level inferences. This obscures meaningful individual differences, limiting the ability to capture nuanced, participant-specific patterns. Here, we use a precision mapping approach to uncover reliable individual signatures of arousal-related FC changes hidden in group-level analyses. We ran two analyses: (1) a group-level analysis of participants with >5 minutes of fMRI data (N = 40, F = 30, μ_{age} = 24.4, σ_{age} = 4.1), and (2) a precision analysis of subjects with >20 minutes of data (N = 3, F = 2, μ_{age} = 30.3, σ_{age} = 4.4). Participants rated arousal for each resting-state scan on a 7-point Likert scale (1 = high, 7 = low). On average, participants completed 29.72 resting-state scans across 4 sessions. Only high (1-2) and low (6-7) arousal runs were kept. fMRI data was preprocessed to align images, denoised, then parcellated into 300 regions of interest (ROI) using the Seitzman atlas. Pearson's pairwise correlations were computed between the averaged ROI time series for each subject. Between subjects, FC matrices were averaged within each condition and compared. We used the Network-Based Statistic to test for significant differences in FC across group conditions.
Group-level results showed increased FC in the dorsal sensorimotor network consistent with prior work ($t(38) = 4.50$, NBS-corrected $p < 0.001$). Precision mapping revealed previously obscured arousal patterns where low arousal was characterized by increased fronto-parietal and decreased auditory network FC. Precision fMRI may reveal stable individual neural correlates of low arousal, allowing targeted care for populations struggling with diminished arousal.

Disclosures: P. Kim: None. **A. Triana:** None. **M. Mitchell:** None. **G. Wulfekuhle:** None. **D.C. Perez Rivera:** None. **Z. Ladwig:** None. **A. Jaimes:** None. **A. Dworetsky:** None. **J. Hernandez:** None. **J. Chernicky:** None. **N.R. Labora:** None. **C. Gratton:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.02/KK59

Topic: I.04. Executive Functions

Support: R01MH118370
NSF CAREER 2502540

Title: Reliability of functional brain network graph metrics: insights from precision mapping

Authors: *A. M. TRIANA[1], M. MITCHELL[2], G. WULFEKUHLE[4], D. C. PEREZ RIVERA[5], Z. LADWIG[6], A. JAIMES[3], A. DWORETSKY[8], J. HERNANDEZ[7], J. CHERNICKY[9], N. R. LABORA[10], C. GRATTON[11];
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Abstract: Graph metrics are used to quantify characteristics of functional brain networks. They are typically computed from 10-minute runs of fMRI data per subject. Reproducibility within individuals is key for detecting meaningful differences in brain network organization that might relate to clinical characteristics. Precision mapping studies that collect large amounts of high-quality data per individual have revealed that estimates of graph metrics such as global efficiency and participation coefficient vary with data quantity, often requiring more than what is commonly collected to be reliable. Yet the reliability of a broader range of graph metrics across data lengths remains to be systematically characterized. Here, we analyze the reliability of a wide range of graph metrics using precision mapping fMRI data from N=87 subjects with more than 80 minutes of data each. Data were preprocessed, denoised, and parcellated into 300 regions of interest using the Seitzman atlas. Pearson correlations were computed between averaged ROI time series. Connectivity matrices were proportionally thresholded at 9 densities ranging from 2% to 10%. We find that: (1) only a subset of metrics reaches 0.8 reliability even with 15-60 min of data (depending on the metric). This subset includes functional connectivity, degree, strength, global efficiency, participation coefficient, and closeness centrality; (2) thresholds have mixed effects, strongly influencing clustering coefficient, local efficiency, modularity, closeness centrality, and integration-segregation difference, while having little impact on other metrics. These findings demonstrate that data quantity critically affects graph metric reliability and may influence the interpretation of differences in brain network organization if data quality and quantity are not carefully controlled, with implications for fMRI studies using graph metrics to derive individual characteristics of brain networks relevant for clinical understanding.

Disclosures: A.M. Triana: None. **M. Mitchell:** None. **G. Wulfekuhle:** None. **D.C. Perez Rivera:** None. **Z. Ladwig:** None. **A. Jaimes:** None. **A. Dworetsky:** None. **J. Hernandez:** None. **J. Chernicky:** None. **N.R. Labora:** None. **C. Gratton:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.03/KK60

Topic: I.04. Executive Functions

Support: NINDS NS124738
NINDS NS075321
NINDS NS097437
NINDS NS097799
Barnes Jewish Hospital Foundation (BJHF)/ ICTS
American Parkinson Disease Association (APDA) Advanced Research Center for PD at WUSTL
Greater St. Louis Chapter of the APDA
Jo Oertli Fund
BJHF (Elliot Stein Family & PD Research Funds)

Title: Precision RSFC improves network fidelity and comparison between Parkinson's disease and healthy controls

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive spread of neuropathology from the brainstem throughout the cortex. This distributed pathology manifests in a complex web of motor, cognitive, and psychiatric symptoms, the neural substrates of which remain poorly understood. This challenge is compounded by substantial interindividual variability in disease progression, therapeutic response, and symptom presentation. Resting-state functional connectivity (RSFC) captured via functional magnetic resonance imaging provides a noninvasive means of mapping the brain's functional architecture and has yielded considerable insight into the network-level disruptions in motor and non-motor systems associated with PD. Conventional paradigms, however, are constrained by limited data quantities that preclude reliable characterization of network organization at the individual level, thereby limiting inferences regarding the neural basis of clinical heterogeneity. The recent emergence of "precision RSFC" predicated on extended (>40 min.) data acquisition has enabled robust identification of individual-specific network topographies and previously inaccessible brain-behavior relationships relevant to PD. In the present research, we examine the utility of precision functional mapping in PD. More than 100 minutes (mean = 118 min.) of low-motion RSFC data were acquired across 3-5 sessions from 35 individuals with PD and 11 healthy

controls, from which individualized network parcellations were derived. Here, we demonstrate that precision RSFC offers improved network mapping fidelity relative to group-level templates, as evidenced by significantly elevated average within-network connectivity in both PD participants (paired t-test: $t(34) = 9.87$, $p < .001$) and healthy controls (paired t-test: $t(10) = 6.47$, $p < .001$). We leverage these individualized parcellations to identify significant group-level differences between PD and healthy controls in both within-network connectivity (predominantly within sensorimotor networks) and between-network connectivity. The influence of data quantity and individualized parcellation on these findings will be further discussed. Collectively, these findings establish the utility of precision RSFC in PD and reveal individual-level network differences that may inform future investigation into the neural substrates of PD.

Disclosures: J. Chernicky: None. **M. Blumenfeld:** None. **A.M. Eid:** None. **L. Rosok:** None. **R.E. Twohy:** None. **C. Gratton:** None. **M.C. Campbell:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.04/KK61

Topic: I.04. Executive Functions

Support: R01MH118370
R01NS124738

Title: Dissociating trait and state variance in the functional brain networks of older adults

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Abstract: In young adults, functional brain networks have been shown to be stable and largely shaped by individual-specific features, rather than state-like factors such as tasks or daily fluctuations (Gratton et al., 2018). However, whether this holds true across the adult lifespan remains unclear. Older adults show greater individual variability in behavioral performance (Christensen, 2001), functional connectivity (FC; Yu, 2023), network modularity (Deery et al., 2022), and network segregation (Chan et al., 2014), suggesting that the variability of network organization may differ with age. In this study, we used precision fMRI data from 55 participants across the adult lifespan (ages 36-74). Notably, we had five MRI sessions per participant, allowing reliable dissociation of stable and state-related network components. Each session consisted of resting-state and task runs, including mental rotation (Dubis et al., 2016) and rhyme tasks (Neta et al., 2014). Behaviorally, we found an age-related increase in response time in both tasks, and a decrease in the task performance in the mental rotation task, but not the rhyme task.

This results map onto past findings reflecting declines of fluid but not crystallized intelligence with age. The coefficient of variation in task performance increased with age in both tasks, suggesting greater within-individual variability in older adults. At the neural level, a data-driven multidimensional scaling (MDS) of pairwise FC correlations revealed clustering by individual and age group, whereas condition-related (rest vs. task) clustering appeared only in high dimensions. We then decomposed FC into group-average, individual, session, and task variance components. Preliminary results show that functional network organization is predominantly shaped by stable, individual-specific factors across the lifespan, replicating prior young adult findings, but the relative contributions of each component varied with age. These findings provide insight into the properties of functional network variability in aging, advancing our understanding of how brain organization is shaped across the lifespan.

Disclosures: Y. Park: None. **M. Mitchell:** None. **D.C. Perez Rivera:** None. **A. Jaimes:** None. **J. Hernandez:** None. **N.R. Labora:** None. **G. Wulfekuhle:** None. **C. Gratton:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.05/KK62

Topic: I.04. Executive Functions

Support: NIH Grant R01MH118370

Title: Precision fMRI reveals differential age-related patterns of desegregation across hubs and networks

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Abstract: Aging is associated with a loss of segregation between distinct brain networks. Connector hubs, or brain regions with strong interactions across multiple networks, play a role in maintaining network segregation in young adults, but it is not clear if connector hubs may play a role in driving age-related network desegregation. Here, in a highly-sampled group of 156 adults spanning 18 to 75 years we implemented precision fMRI approaches to characterize individual-specific functional networks and assess the relationship between connector hubs and desegregation. Importantly, each person had more than 60 minutes of resting-state data, allowing

us to identify individual regions and networks with high reliability, disambiguating individual variability from network segregation properties. We hypothesized three potential models of desegregation: (1) connector hubs increase between-network connectivity, underlying the decreases in segregation in aging, (2) non-hubs increase between-network connectivity and become hub-like, or (3) networks decrease in within-network integrity. As in past reports, we found decreased system segregation with age, particularly in hub regions of association networks (β=-0.24, p=.01) and non-hub regions of sensorimotor networks (β=-0.25, p=.009). In general, hubs exhibited more desegregation with age than non-hubs (β=-0.08, p=.002). For association networks, desegregation was paired with with a robust decrease in within network integrity across age (β=-0.47, p<.001), while hubs decreased in strength (β=-0.28, p=.003) and non-hubs increased in strength (β=0.22, p=.02), consistent with models 2 and 3. Sensorimotor networks non-hubs also had a loss of within network integrity (β=-0.20, p=.03), but this was accompanied by an increase in between-network strength for hubs (β=0.22, p=.02), consistent with models 1 and 3. In sum, we find that desegregation is not a global pattern, but rather is driven by association hubs and sensorimotor non-hubs. Our results provide the greatest support for our hypothesized model 3, that networks decrease in integrity with age, but with a relative sparing of sensorimotor hubs which maintain strong within-network connections across the adult lifespan. These preliminary results suggest that the mechanisms shaping age-related patterns of desegregation across the brain differ between hubs and other regions as well as by network type. These insights are made possible with precision individualized approaches that parse individual variability out of within and between network effects.

Disclosures: M.E. Mitchell: None. **G. Wulfekuhle:** None. **D.C. Perez Rivera:** None. **A. Jaimes:** None. **A. Triana:** None. **Y. Park:** None. **Z. Ladwig:** None. **A. Dworetsky:** None. **J. Chernicky:** None. **N.R. Labora:** None. **J. Hernandez:** None. **C. Gratton:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.06/KK63

Topic: I.04. Executive Functions

Support: MH122066
MH096773
MH129616
MH121518
NS110332
MH121276
MH124567
NS129521
NS088590
Taylor Family Foundation
Intellectual and Developmental Disabilities Research Center

Washington University Hope Center for Neurological Disorders
Basque Government BERC 2022-2025
Spanish State Research Agency: BCBL Severo Ochoa Excellence Accreditation
CEX2020-001010/AEI/10.13039/501100011033
MCIU/AEI/10.13039/501100011033/FEDER, EU

Title: Two novel functional brain networks identified with precision mapping

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Abstract: Recent work using functional MRI (fMRI) has revealed a set of robustly validated large-scale functional networks that are largely conserved across individuals. However, canonical network templates derived from group-average data fail to capture important individual-specific variation and, by definition, cannot identify novel or unknown networks. To find previously undescribed putative functional networks, we developed a precision functional mapping technique that identifies novel functional networks that are not included in current sets of network templates. Using resting-state fMRI data from 28 healthy controls, each with ≥ 2 hours of high-quality data, we identified two novel networks absent from network templates that were consistently observed in each subject. Both networks span spatial boundaries of canonical network templates, suggesting they represent new functional modules rather than sub-networks of known systems. One of these putative new networks is localized to lateral occipital, inferior temporal, and superior temporal regions, and it converges with the social perception network previously identified with task fMRI. Regions of this network overlap with face-selective cortical regions identified by an independent task-based localizer and exhibit functional connectivity with the fusiform face area and the amygdala. These properties distinguish it from the default mode and language networks, despite partial spatial overlap. Meta-analytic reverse inference of the network's spatial distribution associates it with functions including mentalizing, theory of mind, and perception of biological motion and social interactions, suggesting a potential role in integrating visual processing with social behavior. A second novel network, which we term the spatial cognition network, is located in the parieto-occipital junction, retrosplenial cortex, and pars marginalis. Although spatially proximal to the contextual association network, this new network is distinguished by greater functional connectivity with ventral cerebellum and anterior prefrontal cortex. Meta-analytic reverse inference of this network reveals associations with spatial cognition, navigation, and the processing of environmental locations. The novel networks identified here, which are grounded in convergent resting-state functional connectivity and task-based evidence, demonstrate that reliance on predefined canonical network templates can leave meaningful structure in functional brain organization uncharacterized. This work highlights the value of individualized, data-driven approaches to mapping functional brain organization.

Disclosures: A. Dworetsky: None. **D.J. Newbold:** None. **A.N. Nielsen:** None. **R.J. Chauvin:** None. **A. Meyer:** None. **A.Z. Snyder:** None. **S. Marek:** None. **Y. Park:** None. **C. Woo:**

None. **C. Caballero Gaudes:** None. **T.O. Laumann:** None. **N.U.F. Dosenbach:** None. **E.M. Gordon:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.07/KK64

Topic: I.04. Executive Functions

Support: AAN Clinical Research in Parkinson's Award

Title: Precision functional mapping of the voice network

Authors: *L. XAVIER[1], T. O. LAUMANN[2], S. A. NORRIS[2], E. M. GORDON[3]; [1]Washington Univ. in St Louis, Saint Louis, MO; [2]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [3]Radiology, Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Voice production requires coordinated motor and language processes across distributed cortical and subcortical circuits. Dysfunction in this system impairs vocal output and expressive language in neurological disorders. However, current therapies effective in other motor control disorders provide variable benefit for these symptoms, underscoring a critical gap in our understanding of the underlying pathways. Prior work identified two anatomically distinct voice representations in the lateral precentral gyrus, but their circuitry organization and links to language systems remain unclear. We investigated whether these dual voice regions can be mapped reliably at the individual level, whether they connect to individual-specific language networks, and how they integrate into striato-thalamo-cortical and cerebello-thalamo-cortical loops critical for motor control.We used MRI-based precision functional mapping to define the cortical and subcortical architecture of the human voice circuitry in individual participants. Twenty-two healthy adults completed repeated resting-state fMRI sessions, yielding 121 hours of data, and two deeply sampled participants completed additional 80 minutes of task-base fMRI block-design which included vocalization tasks. A novel data-driven resting-state functional-mapping approach identified two spatially separate but connected regions in the lateral precentral gyrus that converged with vocalization-related activity. These regions of interest served as seeds for individual-specific, whole brain connectivity analyses.Both voice regions showed robust, spatially specific connectivity with individually defined cortical language-network regions. They also showed connectivity with striatal and cerebellar territories associated with motor control and language including regions of putamen, caudate, and the anterior and right posterior cerebellar lobes. These patterns support integration of voice regions in primary motor cortex with striato-thalamo-cortical and cerebello-thalamo-cortical motor control loops involved in language and motor coordinationThese findings define an individually organized, language-connected cortico-subcortical functional voice circuitry anchored by dual precentral voice representations. They suggest that segregated somatotopic zones in primary motor cortex serve as integrated regions within multimodal systems supporting voice and expressive language. Such individually defined

maps representing regions associated with vocalization could be used to guide neuromodulatory interventions for voice disorders.

Disclosures: L. Xavier: None. **T.O. Laumann:** None. **S.A. Norris:** None. **E.M. Gordon:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.08/KK65

Topic: I.04. Executive Functions

Support: NIH Grant MH134966

Title: Precision functional mapping of the basal ganglia and thalamus in human neonates

Authors: *S. BLAKE[1], A. LABONTE[1], J. MOSER[2], R. AGARD[1], J. SCANGA[1], M. C. CAMACHO[1], A. NIELSEN[1], D. A. FAIR[2], C. M. SYLVESTER[1];
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Abstract: Anterior parts of the adult basal ganglia (BG) and thalamus (THAL) link to association networks, while posterior parts link to sensorimotor networks. Some regions are highly selective for a single cortical network, while others exhibit integration of multiple networks. Individual variation in the fine-tuning of this organization relates to function and clinical risk, yet the developmental origins remain unknown. Here, we used precision functional mapping (PFM) to characterize the basic organization and selectivity vs. integration of subcortico-cortical functional connectivity (FC) in individual neonates. Greater than 70 minutes of low-motion fMRI data were collected during sleep from 6 healthy, full-term neonates (postmenstrual age at scan: 40.9 - 44.4 weeks). With a winner-take-all (WTA) analysis, each BG and THAL voxel was assigned to the cortical network with which it had the highest FC. We calculated the proportion of voxels linked to sensorimotor vs. association networks. We also used k-means clustering to divide the BG and THAL into regions based on overall FC patterns. For each cluster, we computed a selectivity index (SI), defined as the ratio of FC strength to the preferred network vs. the second preferred network. Higher SI indicated greater selectivity; lower SI indicated greater integration. WTA maps revealed that anterior BG and THAL were most highly connected to association networks, while posterior BG and THAL were most highly connected to sensorimotor networks. A higher proportion of the BG and THAL linked to sensorimotor networks than previously reported in adults or in our prior work using group-average data from neonates: 5/6 subjects exhibited greater sensorimotor representation in both the BG (29-79%) and THAL (85-97%) than the group average (BG: 28%; THAL: 75%). K-means clustering identified 3 regions in the BG and THAL per subject. We found individual differences in cluster FC strength and relative selectivity/integration. For instance, one subject's

most anterior BG cluster was strongly selective for the salience network (FC=0.12, SI: 2.7), while that of another subject showed even stronger salience FC (FC=0.23) but greater integration (SI: 1.6). Our findings suggest that the broad anterior-posterior organization in the subcortex is present by birth. Greater sensorimotor representation in individuals than the group average may reflect current sensory/motor experiences of the neonate and highlights the need for PFM to uncover trends not present in group level results. Future work should determine whether individual differences in association-network selectivity and integration persist or become refined over development.

Disclosures: S. Blake: None. **A. Labonte:** None. **J. Moser:** None. **R. Agard:** None. **J. Scanga:** None. **M.C. Camacho:** None. **A. Nielsen:** None. **D.A. Fair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Turing Medical Inc.. **C.M. Sylvester:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.09/LL1

Topic: I.04. Executive Functions

Title: Population Geometry Separates Shared Dynamics and Individuality in Human Brain Function

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Abstract: Human cognition relies on a functional architecture broadly shared across individuals, yet cognitive abilities and behavioral tendencies vary reliably across people. How a common brain network blueprint gives rise to stable individuality remains unclear. At the neuronal population level, population geometry supports task coding, flexible switching, and memory capacity by organizing neural activity into structured low-dimensional spaces. Here, we investigate whether similar geometric principles operate in whole-brain human fMRI signals to support both shared and individual-specific functional organization. By analyzing resting-state and task fMRI data from 1,200 Human Connectome Project participants, we demonstrate that whole-brain activity patterns organize into a population geometry with separable subspaces for common and individual-specific information. The commonality subspace exhibited canonical large-scale functional organization, including a sensory-association axis and peri-central sensorimotor structure, capturing core features of human brain architecture. By contrast, the individuality subspace revealed more localized, network-specific patterns, indicating that individual differences are expressed through subject-specific recruitment of functional systems. We further examined how this geometry adapts during cognitive task performance. Compared with rest, whole-brain activity during the working memory task showed a significant reduction in effective dimensionality, indicating compression of the population geometric space. Task-related

dynamics concentrated into specific dimensions driven by the coordinated recruitment of prefrontal, parietal, and visual cortices. Crucially, individual expression within this task-specific subspace reflected stable subject-specific organization and predicted individual differences in working memory performance under cross-validation. Together, these findings extend population-level geometric principles from neuronal recordings to human fMRI. Our results suggest that human brain function is organized within a population geometry that segregates common architecture into global dimensions, while isolating stable individuality within separate subspaces. This geometric decoupling may provide a mechanism by which individual variability is expressed without disrupting shared functional organization.

Disclosures: J. Chang: None. **C. Zhou:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.10/LL2

Topic: I.04. Executive Functions

Support: NIH R01AG080137-02

Title: Post-COVID Cognitive Impairment Is Associated with Reduced Executive Network connectivity and Executive-Memory Hyperconnectivity

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Abstract: Post-COVID neurological syndrome produces persistent cognitive impairment in a substantial proportion of survivors, yet its neural basis remains poorly defined. We tested whether post-COVID cognitive impairment reflects domain-specific functional dysconnectivity, with memory and executive networks differentially affected. We analyzed resting-state fMRI data (preprocessed in SPM12 and CONN) from 42 post-COVID participants (74% female; median age 53 years; median 41 months after infection) enrolled in a longitudinal observational study. Participants were classified as cognitively impaired (n=34) or non-impaired (n=8) by neuropsychological testing (NPT). We computed Fisher's z-transformed functional connectivity (FC) for pre-defined region pairs from post-COVID literature within the executive network (middle frontal gyrus, MidFG; lateral prefrontal cortex, LPFC; inferior frontal gyrus, IFG; posterior parietal cortex, PPC) and across circuits linking executive regions to memory regions (hippocampus; posterior parahippocampal gyrus, pPaHC). Group differences were estimated with linear regression adjusted for age and sex, with sensitivity models adding infection severity (hospitalization during infection) and infection history (No. of infection 3+ or not), and a false discovery rate (FDR) correction was applied. Within the executive network, cognitively impaired

patients showed significantly reduced FC: IFG R - MidFG R (beta [SE] = -0.31 [0.12], p = 0.016), PPC R - IFG R (beta [SE] = -0.32 [0.14], p = 0.026), and LPFC L - IFG R (beta [SE] = -0.28 [0.12], p = 0.027). In contrast, cross-circuit connectivity from executive to memory regions was elevated in the impaired group. pPaHC emerged as a convergence hub, showing hyperconnectivity with MidFG R (p=0.003) and PPC R (p=0.005). No significant differences were detected in within-memory connectivity. The pattern is consistent across sensitivity models but does not survive FDR. These exploratory findings suggest that post-COVID cognitive impairment may involve reduced internal coordination within the executive network, accompanied by increased coupling between executive regions and parahippocampal memory-related regions. The executive-to-memory hyperconnectivity may reflect a compensatory response to weakened executive-network integrity. This dysconnectivity pattern offers a candidate network signature for post-COVID cognitive impairment, but validation in larger, more balanced longitudinal cohorts is needed to determine whether it predicts persistent cognitive symptoms or recovery.

Disclosures: E. Lee: None. **M. Maziero:** None. **D. Kramer:** None. **E. Reese:** None. **K. Anderson:** None. **A. Davila-valadez:** None. **A. Kamali:** None. **G. Ortiz IV:** None. **K.M. Hasan:** None. **P. Schulz:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.11/LL3

Topic: I.04. Executive Functions

Support: The Acorn Fund Award (SJK)
NASA TXS0147017 (RID)
NASA 80NSSC25K7298 (RID)
NIH T32DA015036 (WF)

Title: Associations Between Neurochemical Changes and Functional Connectivity Following Sleep Fragmentation in Mice

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Abstract: *Introduction:* Sleep fragmentation is a central feature of several neuropsychiatric disorders, including depression, anxiety, and substance use disorder, and is associated with impaired cognition and emotional dysregulation. Although disrupted sleep has been linked to alterations in both neurochemical signaling and functional brain connectivity, whether and how these processes interact to produce associated behavioral deficits remains poorly understood. *Methods:* C57BL/6J mice (8 male, 8 female) underwent sleep fragmentation in a chamber

consisting of a motorized horizontal sweeping bar that moves continuously from wall-to-wall across the cage floor for 0, 6 (10AM-4PM), or 10 hours (8AM-6PM) per day during the light phase over 5 consecutive days. Mice were assessed using 9.4T high-field fMRI and MRS at three timepoints using a within-subject design: pre-fragmentation baseline, following 6-hour fragmentation, and following 10-hour fragmentation. Resting-state fMRI was used to evaluate seed-to-seed functional connectivity among the anterior cingulate cortex (ACC), insular cortex, and sensorimotor regions (M1, M2, S1, and S2), which were selected based on prominent activation observed prior independent component analyses on the current dataset. MRS was used to quantify excitatory/inhibitory metabolic profile of an ACC voxel and correlated with concurrent changes in functional connectivity.
Results: ACC glutamate and GABA concentrations were strongly correlated across experimental conditions and longitudinal changes ($r=0.92$-0.97, all $p<0.000001$), indicating that animals with changes in glutamate also exhibited changes in GABA. suggesting that sleep fragmentation induces coupled changes in excitatory and inhibitory neurochemical measures. Changes in ACC neurochemistry from baseline to 10-hour, but not 6-hour, sleep fragmentation were associated with alterations in functional connectivity; the strongest relationships involved ACC-centered functional connections, where reductions in glutamate and GABA were both associated with increased connectivity between the ACC and sensorimotor regions (M2-ACC: $r=-0.88$ and $r=-0.91$, respectively). Similar relationships were observed across several additional cortical and insular connections.
Conclusion: Overall, these findings indicate that sleep fragmentation produces coordinated reductions in ACC excitatory/inhibitory neurochemistry that are related to increased ACC-sensorimotor functional connectivity, implicating ACC-centered network reconfiguration as a potential neural mechanism linking disrupted sleep to cognitive and affective dysfunction.

Disclosures: V. Jindal: None. **R.I. Desai:** None. **S.J. Kohut:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.12/LL4

Topic: I.04. Executive Functions

Title: Linking cortico-hippocampal-striatal functional signatures to executive dysfunction in mice following chronic alcohol use

Authors: H. UNSAL[1], M. MARRERO[1], M. RAZIUDDIN CHOWDHURY[1], M. O'BANION[2], A. J. ROBERTS[3], *T. AREFIN[1];
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Abstract: Alcohol use disorder (AUD) is a chronic, relapsing brain disease that causes substantial, lasting executive function (EF) deficits. However, the underlying neurobiological

mechanisms across the spectrum of impairment remain poorly defined, playing a major role in the treatment gap for AUD. Though evidence suggests females may be more susceptible to EF deficits, the impact of sex-based differences and recovery strategies remains understudied. We aim to bridge this knowledge gap by combining resting-state functional magnetic resonance imaging (rsfMRI) with mouse EF monitored via automated group-housing system - IntelliCage, following chronic alcohol exposure in mice. We hypothesize that chronic alcohol exposure will significantly affect hippocampal functional communication with the rest of the brain resulting in substantial EF deficits. Adult male and female C57BL/6J mice underwent chronic alcohol exposure for six weeks using a two-bottle choice every-other-day (EOD) paradigm. Brain functional connectome was assessed using rsfMRI and EF (social interaction, place learning (PL) and reversal PL (RPL)) using the IntelliCage at baseline (pre-EOD) and post-EOD during withdrawal. For PL, each mouse was required to learn a specific, individually assigned corner to access water which was switched to the opposite side during RPL. For both tests, successful trial completion required ≥3 nose pokes within a 5s window with >1 lick on the waterspout. Success ratio was computed as the no. of successful trial completions/ no. of visits in the correct corner. Compared to baseline, success ratio was significantly reduced during post-EOD. A 2×2 ANOVA revealed significant main effect of alcohol on success rate, but not sex or interaction between them. Social interactions were completely abolished in females and reduced in males during withdrawal. Similarly, rsfMRI data revealed significant decrease in the functional connectivity (FC) of the default-mode, limbic, salience, and basal ganglia networks. Specifically, hippocampal-retrosplenial FC - crucial for spatial navigation and decision making and hippocampal-striatal FC - important for the integration of contextual memories with habitual learning to guide goal-directed behaviors, showed significant positive correlations with learning deficits. Additionally, hippocampal-anterior cingulate cortex FC - vital for cognitive control and emotional regulation, showed a significant positive correlation with deficits in social interaction. These findings highlight potential pathways for future research that may guide the development of sex-specific therapeutics to mitigate alcohol-related EF deficits.

Disclosures: H. Unsal: None. **M. Marrero:** None. **M. Raziuddin Chowdhury:** None. **M. O'Banion:** None. **A.J. Roberts:** None. **T. Arefin:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.13/LL5

Topic: I.08. Learning and Memory

Support: HKGRC-GRF 14112423
HKRGC-GRF 14122124
HKRGC-CRF 4012-22G
CityUHK SGP 9380157

Title: Role of parvalbumin interneurons in behavioral adaptation during complex task learning

Authors: X. LIU[1], S. WANG[2], Y. KE[1], ***W. YUNG**[2];
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Abstract: Adaptive behavioral control relies heavily on the prefrontal cortex. As a key prefrontal cortex subregion, the secondary motor cortex (M2) utilizes its extensive connections to integrate motor planning and higher-order cognition. However, it is unclear how information is encoded and regulated by distinct neuronal subtypes in complex tasks. In this study, we utilized two-photon calcium imaging to track parvalbumin (PV) interneurons in M2 of mice by training the subject to perform a Go/No-Go task in the middle of a lever holding action. Behavioral results demonstrated impaired performance when mice switched from the well-learned individual task to this complex task, which however could be gradually improved with training. Imaging result revealed that PV neurons exhibited cue-specific tuning that emerged with the Go/No-Go task training. Further analysis demonstrated that PV neurons exhibited a progressive shift in their activation dynamics over the complex task learning. Significantly, optogenetic activation of PV-neurons to assess its inhibitory influences on the local circuit not only significantly impaired the single-task performance but also that of the combined task during training. When the stimulation was removed, performance gradually improved with training. Together, these findings highlight the potential regulatory roles of PV interneurons within the prefrontal cortex in behavioral adaptation.

Disclosures: X. Liu: None. **S. Wang:** None. **Y. Ke:** None. **W. Yung:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.14/LL6

Topic: I.08. Learning and Memory

Support: NIH Grant ZIAMH002887

Title: Amygdala projections onto parvalbumin-positive cell bodies in prefrontal cortex of the macaque monkey

Authors: ***H. MCARDLE**[1,2], M. K. BALDWIN[2], J. D. FLORES[2], M. A. ELDRIDGE[2], B. J. RICHMOND[3], E. A. MURRAY[2];
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Abstract: Recent studies in our laboratory have revealed significant loss of parvalbumin-positive (PV+) cells within macaque prefrontal cortex after long-standing, selective lesions of the amygdala in the same hemisphere. Studies in rodents have revealed direct projections from the amygdala to PV+ cells, but this has not yet been demonstrated in primates. To address this gap in

knowledge, we injected either the anterograde tracer fluororuby or the anterograde viral tracer lenti-VSV-G hSyn::hM4Di-GFP into the basolateral amygdala of two rhesus macaques (*Macaca mulatta*) to see if terminal boutons colocalized with PV+ cell bodies within the medial (areas 24, 32), orbitofrontal (areas 11, 13 and 14), and ventrolateral (area 12) prefrontal cortex. After tracer or viral transport, brain tissue was collected, cut at 40 microns and saved in a series of 10. One series was processed for Nissl to identify areal borders within cortex and to help in reconstructing injection site locations within the amygdala. Additional series were processed to reveal tracer/viral label and parvalbumin using immunohistochemical techniques. Colocalization of terminal label onto PV+ cell bodies was assessed using both bright-field and confocal microscopy. We found colocalization of amygdala terminal label with PV+ cells within each of the cytoarchitectonic fields examined: areas 24, 32, 11, 13, 14, and 12. Terminal label was typically found directly on PV+ cell bodies or along proximal dendrites immediately adjacent to the PV+ cell body. This finding suggests that the amygdala has a direct influence on the activity of PV+ cells within prefrontal cortex.

Disclosures: H. McArdle: None. **M.K. Baldwin:** None. **J.D. Flores:** None. **M.A. Eldridge:** None. **B.J. Richmond:** None. **E.A. Murray:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.15/LL7

Topic: I.08. Learning and Memory

Support: ZIAMH002887

Title: Complete loss of parvalbumin-immuno-positive cells within cortical areas 9 and 12 after long-standing lesions of the amygdala and medial prefrontal cortex in macaque monkeys

Authors: *M. K. BALDWIN[1,2], H. MCARDLE[2], J. D. FLORES[3], E. A. MURRAY[2];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Lab. of Neuropsychology, NIMH, NIH, Bethesda, MD; [3]NIMH, Brigham Young Univ., Tumwater, WA

Abstract: Lesion studies provide a unique opportunity to identify network related changes associated with brain damage or disease and potential insight into normal network interactions. We evaluated the brains of three rhesus monkeys (*Macaca mulatta)* that had received lesions to the amygdala in one hemisphere and the anterior cingulate cortex (ACC: areas 24 and 32) in the opposite hemisphere 9-10 years prior to tissue analysis. Specifically, we assessed the ventrolateral and dorsomedial prefrontal cortex ipsilateral to the amygdala lesion and contralateral to the ACC lesion and compared these results to those from 2 age- and sex-matched controls. Brains were cut coronally in a series of 10 at a thickness of 40 microns on a freezing microtome. One series was stained for Nissl to reveal laminar and areal borders, while another series was reacted for parvalbumin (PV), a calcium-binding protein often expressed in

inhibitory interneurons within the cortex. Our results showed significant changes to the quantity of PV+ cells within prefrontal cortical areas 9 and 12 in hemispheres with amygdala lesions compared to intact (control) hemispheres. Within area 12, we found two regions with complete loss of PV+ cells: the regions extended through all layers and were found consistently within 12r and portions of 12l and 12o. Portions of area 9 showed similar patterns of absent PV+ cells across all layers of cortex. These observations suggest profound changes to neuronal activity within areas 9 and 12 after long-standing lesions of the ipsilateral amygdala and contralateral ACC, and highlight the strong interactions between these structures in intact animals.

Disclosures: M.K. Baldwin: None. **H. McArdle:** None. **J.D. Flores:** None. **E.A. Murray:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.16/LL8

Topic: I.08. Learning and Memory

Support: ZIA DA000642

Title: Formation and utilization of abstract task representations for generalization

Authors: *A. R. VAIDYA[1], N. MOUSSA[1], T. KHAN[2], D. BADRE[3], T. KAHNT[4];
[1]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [2]Northwestern Univ., Chicago, IL; [3]Carnegie Mellon Univ., Pittsburgh, PA; [4]Cell. and Neurocomputational Systems Br., NIH, NIDA IRP, Baltimore, MD

Abstract: Sudden unpredictable disruptions in the environment can make tried and true action plans suddenly obsolete, or even actively harmful. In such situations, previous related experiences can provide useful templates for guiding future actions. Abstract task representations that bridge novel problems and previous experience are thought to facilitate the transfer of knowledge, speeding learning and facilitating adaptive behavior. Here, we used fMRI to test the neural processes by which such abstract task representations form and are utilized during generalization. Eighteen participants completed an acquired context equivalence task over multiple sessions while in the scanner. In each session, participants had to learn how contexts could be clustered together based on shared stimulus-reward associations to solve a generalization test where they were presented with novel conditions without feedback. We find distinct circuits representing abstract task information at different phases of this task. While subjects discovered the abstract task structure during initial training, a corresponding representation emerged in the hippocampus. In contrast, the orbitofrontal and frontoparietal cortex maintained this information when it was used to make novel inferences during generalization. Trial-by-trial fluctuations in the strength of these abstract task representations were correlated with reactivation of contexts linked by the abstract task structure within the

ventral visual cortex. These results shed new light on the neural mechanisms by which abstract task representations are formed and used for adaptive behavior in novel settings.

Disclosures: A.R. Vaidya: None. **N. Moussa:** None. **D. Badre:** None. **T. Kahnt:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.17/LL9

Topic: I.04. Executive Functions

Support: F31 DA060673
R00 DA049886
R01 DA058666
R01 DA011792
R01 DA043204

Title: Relationship between sleep parameters and intra-dimensional/ extra-dimensional attentional set-shifting cognitive performance in adult rhesus monkeys

Authors: *D. A. BORGATTI, L. F. BERRO;
Neurosci., Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: This study sought to investigate the relationship between baseline actigraphy-based sleep quality and cognitive performance in adult rhesus monkeys, a species that shares similar sleep-wake cycles with humans. Six adult rhesus monkeys (2 females, 4 males) ages 14-22 were trained on an intra-dimensional/ extra-dimensional attentional set-shifting (ID/ED) task using the Cambridge Neuropsychological Test Automated Battery (CANTAB) apparatus. The ID/ED task has been proposed as a measure of executive functioning that evaluates attentional set-shifting (i.e. the ability to switch between arbitrary internal rules guiding behavior) and perseverative responding. The task is comprised of 8 stages of increasing difficulty: simple discrimination (SD), simple discrimination reversal (SDR), compound discrimination (CD), compound discrimination reversal (CDR), intra-dimensional shift (ID), intra-dimensional shift reversal (IDR), extra-dimensional shift (ED), and extra-dimensional shift reversal (EDR). Actigraphy-based sleep parameters were recorded during baseline (dark phase from 18h to 6h), and baseline sleep parameters were compared to the subjects' performance on a baseline ID/ED task conducted between 11h and 15h at least 2 months after initial training. Our findings show that % wake and sleep efficiency were significantly correlated with total errors, total perseverative errors, and total trials to completion in the ID/ED task. Increased % wake and decreased sleep efficiency were associated with greater errors, greater perseverative errors, and higher number of trials to completion. Sleep efficiency and % wake also were significantly correlated with errors during the SDR and ED stages, perseverative errors during the SDR and CDR stages, and total trials to completion during the ED stage. Sleep fragmentation was significantly correlated with

mean accuracy during the SD stage while sleep latency was significantly correlated with mean accuracy during the EDR stage. Increased % wake and decreased sleep efficiency were associated with greater errors, greater perseverative errors, and higher number of trials to completion while increased sleep fragmentation and increased sleep latency were associated with lower stage accuracy. These findings show that sleep quality directly influences cognitive functioning in rhesus monkeys. Different sleep parameters correlated with different cognition-related measures, in total as well as during particular stages of the task, suggesting a complex relationship between sleep and cognition.

Disclosures: D.A. Borgatti: None. **L.F. Berro:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.18/LL10

Topic: I.04. Executive Functions

Support: Psi Chi Graduate Research Grant (OZ)

Title: Dose-dependent effects of ventral hippocampal muscarinic receptor blockade on instrumental performance and set-shifting

Authors: W. ZHANG[1], M. JOHANSEN[1], M. OCHO[1], M. F. STANFIELD[1], Y. TANG[1], S. B. FLORESCO[2], ***W. E. PRATT**[1];
[1]Psychology, Wake Forest Univ., Winston Salem, NC; [2]Psychology, Univ. British Columbia, Vancouver, BC, Canada

Abstract: Set shifting, a form of behavioral flexibility, requires individuals to adapt their behavior in response to changing rules in the environment. Previous research has shown that the ventral hippocampus is important for successful set-shifting. Specifically, ventral hippocampal inactivation impaired rats' ability to shift between allocentric and egocentric strategies in a cross-maze task by increasing perseverative errors, suggesting that this region may support the suppression of previously rewarded response strategies (Torres-Berrío et al., 2019). However, the receptor-level mechanisms supporting this contribution remain poorly understood. Given the proposed role of acetylcholine in modulating memory encoding and retrieval within cortico-hippocampal circuits, the present study examined the role of ventral hippocampal muscarinic acetylcholine receptors in an operant set-shifting task. Male Sprague-Dawley rats (N = 12/group) underwent surgery to implant bilateral cannulas above the ventral hippocampus and were trained to lever press for sucrose reinforcement. On the drug test day, the appropriate strategy for reinforcement was shifted from pressing a lever based upon a learned response rule (pressing the lever opposite their side preference) to a visual cue rule (pressing the lever below an illuminated stimulus light). In the first experiment, blocking ventral hippocampal muscarinic receptors with 10 μg/side of scopolamine methyl bromide led to significant performance deficits in responding,

including increased latency to lever press, $t(15) = -10.04$, $p < .001$, $d = -4.95$, and omission of trials, Welch's $t(6.00) = -10.12$, $p < .001$, $g = -5.74$. However, rats that successfully completed the task (N = 7) trended toward a faster shift to the visual cue rule compared to the vehicle group, as demonstrated by fewer trials to criterion, $t(15) = 1.97$, $p = 0.068$, $d = .97$ and errors to criterion, $t(15) = 1.92$, $p = 0.074$, $d = .95$. To follow-up on this trend, Experiment 2 replicated the experiment with a lower dose of scopolamine in a separate group of rats (1 μg/side). At this dose, muscarinic receptor blockade did not increase omissions or response latencies relative to control. However, rats no longer showed a tendency to shift to the visual cue-based strategy more quickly than controls (trials to criterion: Welch's $t(16.98) = -.20$, $p = .845$, $g = -.08$; errors to criterion: Welch's $t(15.35) = -.61$, $p = .554$, $g = -.24$). Overall, these findings indicate that ventral hippocampal muscarinic receptor blockade, at doses that did not cause general behavioral impairment, also did not affect rats' ability to shift from a response-based to a visual cue-based strategy.

Disclosures: W. Zhang: None. **M. Johansen:** None. **M. Ocho:** None. **M.F. Stanfield:** None. **Y. Tang:** None. **S.B. Floresco:** None. **W.E. Pratt:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.19/LL11

Topic: I.04. Executive Functions

Support: This material is based upon work supported by the Department of War (DoW) Small Business Innovation Research (SBIR) Program under Contract No. FA238423PB017.

Title: Real-time closed-loop neurostimulation and multi-modal biosensing enhances cognitive performance in virtual reality-based cognitive tasks

Authors: Z. STEINE-HANSON[1], M. MAHMOOD[1], M. DARROW[2], A. COVALIN[2], N. KHODAPARAST[2], J. ARTUSO[1], *C. RUSSOMANNO[1];
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Abstract: Human performance in demanding virtual environments depends on the ability to sustain attention, regulate stress, and adapt cognitive control in real time. While prior work in brain-computer interfaces and neurostimulation has shown early evidence of performance enhancement, many existing systems rely on open-loop interventions, post-hoc performance measures, or cumbersome unimodal sensors that provide limited context about the user's cognitive state. Closed-loop neural interfaces that combine wearable multimodal sensing with real-time intervention may offer a more adaptive approach to supporting performance during immersive task engagement. In this work, we developed and evaluated a wearable closed-loop neural interface that uses continuous multimodal biosensor data to estimate attention, stress, and

cybersickness and deliver targeted, real-time neurostimulation during virtual reality tasks. Validated in a clinical trial comprising over 200 sessions across 45 participants, the system demonstrated broad deployment across diverse demographics, including a range of racial groups, gender, anatomies and hairstyles without requiring significant hardware or protocol modifications. The resulting dataset provides evidence that closed-loop neurostimulation can reduce virtual reality cybersickness symptoms, sustain attention during continuous monitoring, and improve performance among the lowest-performing participants. Together, these findings suggest that closed-loop neurostimulation can enhance executive performance in immersive environments and provide a foundation for adaptive training systems that respond to the user's cognitive state in real time.



Disclosures: Z. Steine-Hanson: A. Employment/Salary (full or part-time):; OpenBCI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OpenBCI, Inc. **M. Mahmood:** A. Employment/Salary (full or part-time):; OpenBCI, Inc. **M. Darrow:** A. Employment/Salary (full or part-time):; Spark Biomedical. **A. Covalin:** A. Employment/Salary (full or part-time):; Spark Biomedical. **N. Khodaparast:** A. Employment/Salary (full or part-time):; Spark Biomedical. **J. Artuso:** A. Employment/Salary (full or part-time):; OpenBCI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OpenBCI, Inc. **C. Russomanno:** A. Employment/Salary (full or part-time):; OpenBCI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OpenBCI, Inc..

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.20/LL12

Topic: I.04. Executive Functions

Support: R01MH131637

Title: Negative Feedback-Related Medial Frontal Cortex Theta Activity and Memory for Feedback-Associated Social Stimuli in Social Anxiety

Authors: *K. HOSSEINI[1], J. PETTIT[1], A. MATTFELD[2], G. BUZZELL[1];
[1]FLORIDA INTERNATIONAL Univ., Miami, FL; [2]Psychology, Florida Intl. Univ., Miami, FL

Abstract: Social anxiety (SA) is associated with enhanced error monitoring, which refers to the ability to self-detect one's own mistakes. One hypothesis is that stronger error monitoring contributes to the maintenance/worsening of SA by strengthening the encoding of error events (including relevant social cues present when errors occur), negatively biasing what is remembered. In prior work, we linked MFC theta oscillations during error processing—specifically the processing of self-detected errors in a Flanker task—to subsequent memory biases in individuals with high SA symptoms. This raises an important question: does this neurocognitive mechanism generalize beyond self-detected errors to other forms of negative performance events, such as the processing of external error feedback? Extending to feedback processing is particularly important, as the neural mechanisms underlying self-detected error monitoring and external feedback processing are highly overlapping anatomically and in their reliance on frontal theta oscillations, and external negative feedback may better model the external evaluative contexts also salient in SA. Therefore, we employed a time-estimation task with performance feedback to investigate neural responses to externally provided negative performance signals. While EEG was recorded, 70 participants completed a time-estimation task with trial-unique faces, followed by a surprise memory test. Similar to prior studies of self-detected errors, we found that higher SA was associated with greater error-related MFC-posterolateral theta connectivity ($p = .004$), although only when depression severity was low. However, we found no relationship between SA severity and the memory bias for negative events ($p = .71$). Similarly, we found no relationship between MFC-posterolateral theta connectivity and the memory bias for negative feedback events ($p = .86$). Taken together, these findings demonstrate that SA is associated with enhanced MFC-posterolateral theta connectivity in response to either self-detected errors or external negative feedback. However, associations with memory biases for self-detected errors do not appear to similarly generalize to the processing of external negative feedback. Mechanistic interpretations of these findings will be discussed.

Disclosures: K. Hosseini: None. **J. Pettit:** None. **A. Mattfeld:** None. **G. Buzzell:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.21/LL13

Topic: I.04. Executive Functions

Support: R01MH131559

Title: Task representations in a community structure

Authors: *B. HUANG[1], J. JIANG[2];
[1]Univ. of Iowa, Iowa, IA; [2]Psychological & Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Cognitive flexibility enables us to switch between different tasks to accommodate changing goals. Previous studies have shown that the brain can learn the probability of switching in general and the probability of switching to a specific task to facilitate cognitive flexibility. Beyond first-order statistical relations, in real life tasks usually form higher-order structures. For example, tasks can group into communities (i.e., clusters of tasks with more frequent switches within than between clusters). However, it remains unknown whether and how task communities can be learned to support cognitive flexibility. Here, participants (n = 40) switched between tasks at the trial level in a task switching paradigm with eight perceptual discrimination tasks. Unbeknownst to the participants, the tasks are organized into two communities of four tasks each. Within each community, only one task (boundary task) has 1/3 chance to switch to the boundary task of the other community, while all other task switches are non-boundary tasks that can only switch to tasks in the same community. Behaviorally, we focused on boundary tasks and found that participants responded more slowly and made more errors when switching across communities compared with switching within communities. Univariate analyses revealed stronger activation in the Posterior Cingulate Cortex (PCC) and Cerebellum, for across- than within-community task switches while the opposite pattern in the right anterior hippocampus. These results demonstrate that the brain can learn task community structure. To investigate how the brain represents task communities, we tested two competing hypotheses. The community reorganization hypothesis posits that all tasks in the same community are represented more closely. The boundary separation hypothesis states that only boundary tasks are separated, while non-boundary tasks are not affected. Pattern similarity analysis revealed that the frontoparietal network, including dorsolateral prefrontal cortex (dlPFC) and intraparietal sulcus (IPS), showed a community effect for boundary tasks, such that their fMRI activation patterns were more similar to those of tasks from the same community than different communities. However, this effect was absent for non-boundary tasks. Trail-level brain-behavioral analysis showed that higher pattern similarity between tasks was associated with more similar performance. Our findings suggest that the brain can learn the task community structure and provide empirical evidence supporting the boundary separation hypothesis on the relationship between community tasks to influence performance in cognitive flexibility.

Disclosures: B. Huang: None. **J. Jiang:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.22/LL14

Topic: I.04. Executive Functions

Title: A Comprehensive Model for the Effects of Variations in Iron Levels on Neural and Cognitive Function: Initial Results

Authors: *M. J. WENGER[1], J. T. TOWNSEND[2], S. F. NEWBOLDS[3];
[1]Cell. & Behavioral Neurobio., Univ. of Oklahoma, Norman, OK; [2]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [3]Cell. & Behavioral Neurobio., The Univ. of Oklahoma, Norman, OK

Abstract: Decades of research in humans and in animal models have documented the range of negative impacts of low iron levels, including iron deficiency, with and without anemia. In humans (infants, adolescents, and women) these include negative impacts on physical, perceptual, and cognitive performance, running from basic perceptual encoding to effects on various aspects of memory and more complex cognitive function such as categorization. At the neural level, effects have been documented on neural physiology and function, running from synthesis and regulation of neurotransmitters to large-scale neural dynamics related to cognitive performance. The range of roles played by iron in the central nervous system---including myelination, neurotransmitter synthesis and regulation, synapto- and neurogenesis, and energy expenditure---poses a challenge to any attempt to provide a comprehensive and integrative account of these effects. We describe such an approach, based on information-theoretic conceptions of the boundary conditions on idealized communication systems, originally proposed by Shannon (1959) and Slepian (1963). This approach relies on a set of critical quantities, including: *A*, the signal/noise ratio of the system; *R*, the transmission rate of information within the system; *n*, the number of coding/decoding elements within the system; and *M*, the complexity of the code involved. We suggest that *A* can be conceptualized as a function of the integrity of the neurotransmitters involved, determined by the relative level of serum ferritin (sFt), soluble transferrin receptor (sFt), and their ratio (total body iron, TBI); *R* reflects the rate of neural activity, determined by the relative levels of the variables associated with oxygen transport (hemoglobin, hematocrit, mean corpuscular volume, red blood cell distribution width); *n* is the size of the neural population supporting a response, determined by the combination of variables associated with neurotransmitters and oxygen transport; and *M* is a task variable determined by empirical stimulus entropy. We compare the predictions of this model to extant human cognitive and electrophysiological data and show that this comprehensive information-theoretic account is empirically consistent with experimental data and point to novel theoretical and empirical challenges requiring future work.

Disclosures: M.J. Wenger: None. **J.T. Townsend:** None. **S.F. Newbolds:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.23/Web Only

Topic: I.04. Executive Functions

Title: Assessing broad cognitive abilities in young adults with the Vienna test system: A correlation-based pilot study

Authors: *H. KIM, K. SCHMITT;
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Abstract: Genetic factors initially determine the brain's physical characteristics, but environmental experiences and nutrition continue to modify neural structure throughout childhood and adolescence [1]. Cognitive functions are referred to as acquiring information, internal processing, and generating behavioral responses. Comprehensive cognitive assessment examines higher cortical functions, including memory, attention, language, executive function, and praxis. It is essential for identifying clinical syndromes such as dementia, delirium, and depression [2]. This pilot study focused on healthy young adults to characterize their cognitive-performance profile and examined the structure of cognitive functioning using correlation analysis. Ten university students (5 males, 5 females with a mean age of 20.92 ± 0.51) completed the Cognitive Basic Assessment (COGBAT) of the Vienna Test System. It is a standardized and computerized cognitive test battery consisting of validated subtests of 1) attention and processing speed, 2) working memory, 3) executive function, and 4) information processing. Descriptive statistics and independent samples t-tests were conducted; however, no meaningful group differences were revealed, which were likely due to the small sample size. Pearson correlations were used to examine relationships among cognitive domains, with statistical significance set at $p < 0.05$. Two major cognitive clusters emerged. First, a highly coherent memory-centered cognitive network was observed. The COGBAT index demonstrated strong positive correlations with Figure Memory (r = .933), Learning (r = .893), Short Recall (r = .895), Long Recall (r = .926), and Recognition (r = .744). Second, executive-function measures formed a separate cluster. Executive Function correlated significantly with Cognitive Flexibility (r = -.660) and Planning (r = .686), but showed minimal associations with memory or attention. Findings indicate that healthy young adults exhibit a strongly integrated memory-centered cognitive network. These memory-related measures also showed robust correlations with the global cognitive index, as a central feature of global cognitive performance. Executive Function, including cognitive flexibility, planning, and response inhibition, showed minimal associations with memory or attention. This pattern demonstrates reduced variability and ceiling effects among healthy young adults, which are commonly observed [3] and, therefore, future studies with larger samples are needed to examine potential sex-linked patterns and developmental or clinical deviations from normative cognitive structure.

Disclosures: H. Kim: None. **K. Schmitt:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.24/LL15

Topic: I.04. Executive Functions

Support: IDEICE Grant 01-2025

Title: Psychometric validation of a digital executive function assessment tool for primary school children in the Dominican Republic

Authors: *H. M. MARTE-SANTANA, D. CUBILLA-BONNETIER, E. REYNOSO-ARELLANO, L. V. SÁNCHEZ-VINCITORE;
Univ. Iberoamericana, Santo Domingo, Dominican Republic

Abstract: Executive functions (EF) are higher-order cognitive processes that support goal-directed behavior, behavioral regulation, and cognitive performance. However, EF assessment in educational contexts is often limited by the logistical demands of laboratory-based paradigms. This study evaluated the psychometric properties of the Juego de Evaluación de las Funciones Ejecutivas (JEFE), a self-administered Android application designed to assess inhibitory control, working memory, and cognitive flexibility in primary school children. JEFE integrates three established behavioral paradigms: a Go/No-Go task, a 2-back task, and a Card Sorting task. The sample included 1,166 third- and fourth-grade students from public and private schools across four educational regions of the Dominican Republic. Task performance was characterized using accuracy and reaction-time indicators. Internal consistency was estimated using McDonald's omega, Cronbach's alpha, and split-half reliability, and known-groups validity was examined through grade-level comparisons. Reliability was adequate across tasks, with the highest internal consistency for inhibitory control ($\omega = .886$; $\alpha = .886$; split-half = .898), followed by working memory ($\omega = .803$; $\alpha = .803$; split-half = .791) and cognitive flexibility ($\omega = .770$; $\alpha = .770$; split-half = .797). Grade-level comparisons showed small but significant differences in Go-trial reaction time, No-Go accuracy, and regular-trial accuracy in the cognitive flexibility task, whereas working-memory indicators did not differ significantly between grades. These findings suggest that JEFE provides a reliable and scalable approach for collecting standardized behavioral markers of executive functioning in real-world school settings. The platform may support large-scale neurocognitive assessment in Latin American educational contexts and facilitate future studies examining how executive control contributes to learning and developmental outcomes.

Disclosures: H.M. Marte-Santana: None. **D. Cubilla-Bonnetier:** None. **E. Reynoso-Arellano:** None. **L.V. Sánchez-Vincitore:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.25/LL16

Topic: I.04. Executive Functions

Title: Proactive control enhances incidental memory by preserving the representational fidelity of encoded items

Authors: *F. GENG[1], C. GAO[2], H. ZHOU[3], W. XU[4], Y. HU[2];
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Abstract: Much of human memory forms incidentally, as we process information without any intention to remember. Such incidental encoding unfolds within continuously shifting modes of cognitive control: proactive control, in which goals and rules are activated before a stimulus arrives, and reactive control, in which task-relevant features are selected only after stimulus onset. How these modes shape incidental memory, and the neural representational mechanisms involved, remain poorly understood. Drawing on engram theory, we hypothesized that the control mode regulates the fidelity of item-specific neural representations during encoding, thereby determining whether memories endure. A localizer functional MRI (fMRI) task (n = 15) first generated cross-subject neural templates for 160 pictures. An independent sample (n = 88; 40 females, 48 males; mean age 23.0 years) then classified these pictures under proactive or reactive control inside the scanner, followed 15 minutes later by a surprise recognition test. Cross-subject representational similarity analysis quantified target representational fidelity (RF) on each trial, and multivariate decoding indexed cue and rule representations. Proactive control produced better memory than reactive control (memory d', paired $t(87) = 6.42$, $p < .001$), with comparable classification accuracy across modes. Target RF was higher for remembered than forgotten items in visual-temporal and frontal regions ($t(87) = 3.96$ and 2.93, both $p < .005$) and positively predicted memory at the trial level ($\beta = 0.19$, $p < .001$). Mediation analysis showed that target RF partially mediated the effect of control mode on memory. Critically, cue representations were stronger under reactive control and negatively related to target RF ($\beta = -0.023$, $p = .027$); a serial mediation confirmed that reactive control elevated cue decodability, which reduced target RF and impaired memory. Rule representations, decodable in frontal cortex, were likewise negatively associated with target RF. Thus, cognitive control modes shape incidental memory by tuning the fidelity of item representations, with reactive control inducing representational competition among co-occurring cues, rules, and targets. We propose a representational framework in which cognitive control actively governs neural representations and memory emerges as their downstream consequence.

Disclosures: F. Geng: None. **C. Gao:** None. **H. Zhou:** None. **W. Xu:** None. **Y. Hu:** None.

Poster

PSTR246: Executive Function and Learning

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR246.26/LL17

Topic: I.04. Executive Functions

Title: Gastrointestinal Symptoms Are Associated With Reduced Executive Function in Nursing Students: Evidence Supporting Gut-Brain Interactions in Young Adults

Authors: *L. E. LUNA-VILLEGAS[1], N. Y. CORTÉS[2];
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Abstract: Introduction: The gut-brain axis has emerged as a key bidirectional communication system linking gastrointestinal functioning with cognitive and emotional processes. Psychological distress and sleep disturbances have been associated with gastrointestinal symptom burden, which may negatively affect executive functioning through autonomic, endocrine, immune, and neural pathways. Although these relationships have been documented in clinical populations, evidence in healthy young adults remains limited. This study examined associations among perceived stress, anxiety, sleep quality, gastrointestinal symptoms, and executive function in nursing students exposed to sustained academic demands.**Methods:** A cross-sectional correlational study was conducted in 81 nursing students from a public university in Mexico (mean age = 19.84 ± 1.74 years; 86.4% female). Participants completed validated measures of perceived stress (PSS-14), trait anxiety (STAI-T), sleep quality (PSQI), and gastrointestinal symptoms (GSRS). Executive functioning was assessed using the Neuropsychological Battery of Executive Functions and Frontal Lobes (BANFE-3). Pearson correlations and hierarchical multiple regression analyses were used to examine relationships among psychological, physiological, and cognitive variables.**Results:** Perceived stress ($r = 0.31$, $p < 0.05$), trait anxiety ($r = 0.21$, $p < 0.05$), and poor sleep quality ($r = 0.28$, $p < 0.05$) were positively associated with gastrointestinal symptom severity. Gastrointestinal symptoms were negatively associated with executive function performance ($r = -0.28$, $p < 0.05$), while perceived stress was also negatively associated with executive function ($r = -0.35$, $p < 0.05$). Hierarchical regression analyses supported the contribution of executive functioning beyond psychological and gastrointestinal variables.**Conclusions:** The findings suggest that gastrointestinal symptoms may be associated with reduced executive functioning in young adults, supporting the role of the **gut-brain axis** in cognitive health. Gastrointestinal disturbances, stress, and poor sleep may affect attention, inhibitory control, cognitive flexibility, and planning, highlighting the need for further neuroscience research to better understand the biological mechanisms linking gastrointestinal health and cognitive performance.

Disclosures: L.E. Luna-Villegas: None. **N.Y. Cortés:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.01/LL18

Topic: I.08. Learning and Memory

Support: 2019R1A2C2088799
2022M3E5E8017723
RS-2024-00452391
RS-2025-02303740
Mid-Career Bridging Program through Seoul National University

Title: Prelimbic and infralimbic cortex differentially contribute to hippocampus-dependent spatial context working memory

Authors: *H. HA[1], E.-H. PARK[1], I. LEE[2];
[2]Brain and Cognitive Sci., [1]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Although interactions between the hippocampus and medial prefrontal cortex (mPFC) are critical for working memory (WM), their precise neural dynamics remain poorly understood. The infralimbic cortex (IL) receives denser projections from the intermediate hippocampus (iHP) than the prelimbic cortex (PL), suggesting a functional gradient within mPFC. Here, we examined IL and PL neural dynamics with respect to iHP activity in male Long-Evans rats (n = 5) performing a VR-based spatial context WM task on a cylindrical treadmill surrounded by LCD monitors. During the sample phase, rats were exposed to one of four VR contexts (Forest, City, Indoor, Mushroom), followed by a 3-s delay, after which correct licks were rewarded (120 trials/session). The iHP was inactivated with muscimol (0.3-0.5 μL/site) while single-unit activity was recorded simultaneously in PL and IL using 24 tetrodes. iHP inactivation significantly reduced WM accuracy from 84% to 62% ($p < 0.001$). Ongoing control experiments indicate that (1) partial cue removal did not impair performance, supporting reliance on holistic scene configuration, and (2) inactivation caused minimal impairment when choices were made within the scene, suggesting that iHP primarily binds scene experience into a coherent representation rather than serving as a real-time visual relay. Single-unit analyses revealed that neurons in both PL and IL were modulated by context and choice during the sample and delay phases. However, iHP inactivation differentially altered these responses: PL showed selective changes in context-driven activity ($p < 0.01$), whereas IL exhibited reduced modulation by both context ($p < 0.05$) and choice ($p < 0.01$), with choice modulation further diminished during the delay ($p < 0.001$). Notably, 9.5% of IL neurons encoded choice across both task phases, whereas 13.3% of PL neurons conjunctively encoded both context and choice. Together, these findings suggest that iHP binds complex spatial context into coherent representations and transmits them to mPFC, where they are maintained by intrinsic prefrontal mechanisms. Within this iHP-dependent framework, PL acts as an integrative repository for context and choice, whereas IL preferentially supports the temporal organization of choice-related information.

Disclosures: H. ha: None. **E. Park:** None. **I. Lee:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.02/LL19

Topic: I.08. Learning and Memory

Support: NRF 2019R1A2C2088799
NRF 2022M3E5E8017723
NRF RS-2024-00452391
NRF RS-2025-02303740
Mid-Career Bridging Program through Seoul National University

Title: The intermediate, but not dorsal, hippocampus critically encodes negative valence during spatial navigation in virtual reality

Authors: *H. HWANG, I. LEE;
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Abstract: The hippocampal cognitive map integrates spatial and non-spatial representations, such as value. We previously reported that the dorsal (dHP) and intermediate hippocampus (iHP) play differential roles in value-based navigation with different reward magnitudes (Hwang et al., 2024). However, this prior work shared a common limitation with most value-related studies: it focused exclusively on positive valence, which does not reflect how animals process opposing valences in natural environments. To address this, we extended our framework to include both positive and negative valences, aiming to further dissociate dHP and iHP contributions to spatial and valence representations. We bilaterally inactivated the dHP or iHP in body-fixed rats (n = 5, ongoing) performing an approach-avoidance navigation task in virtual reality. Rats were trained to run on a cylindrical treadmill along a circular track containing two unmarked zones, each occupying one-sixth of the track and associated with either a reward (32% sucrose) or an aversive stimulus (0.1 mM quinine). To maximize hippocampal engagement, the location of the sucrose zone alternated daily between two candidate positions. Well-trained rats exhibited a significant preference for the sucrose zone and active avoidance of the quinine zone. Preliminary results comparing bilateral inactivation of the dHP or iHP within the same animals revealed that both manipulations reduced accuracy in locating the sucrose zone relative to control conditions. However, only iHP inactivation resulted in a trend toward increased visits to the quinine zone, suggesting the iHP plays a greater role in spatial representations associated with negative valence. Stop-location analysis further confirmed the zonal visit patterns. Both dHP and iHP inactivations decreased the proportion of stops in the sucrose zone, but only iHP inactivation increased the proportion of stops in the quinine zone. In addition, both inactivated groups showed an increase in overall stopping behavior, suggesting less efficient navigation. Navigational accuracy, quantified by angular deviation from the sucrose zone center and mean vector length, was impaired under both conditions. Notably, direct comparisons between the two experimental conditions revealed that iHP-inactivated rats exhibited significantly distinct angular distributions and mean directions compared to dHP-inactivated rats. Overall, these findings suggest that while both the dHP and iHP are important for precise navigation toward locations associated with positive valence, the iHP is critically involved in processing negative valence during valence-based navigation.

Disclosures: H. Hwang: None. **I. Lee:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.03/LL20

Topic: I.08. Learning and Memory

Support: NRF 2019R1A2C2088799
NRF 2022M3E5E8017723
NRF RS-2022-NR075250
NRF RS-2024-00452391
NRF RS-2025-02303740
the Mid-Career Bridging Program through Seoul National University

Title: Flexible encoding of task structure in the subiculum during virtual navigation

Authors: *S.-M. LEE, I. LEE;
Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Goal-directed navigation depends on flexible representations that go beyond precise spatial encoding to incorporate the structure of a task. Although hippocampal place cells provide detailed positional information, repeated experience may promote a more schematic organization of space centered on behaviorally relevant goals. Based on prior evidence showing schematic firing patterns in the subiculum across environments and trajectories, we hypothesized that the subiculum encodes such structure-based representations. To test this idea, we developed a virtual reality task in which male Long-Evans rats (n=5) navigated a circular track to obtain a reward. On each trial, rats were teleported to one of three start locations in a pseudorandom sequence and then navigated to a fixed reward site. At the reward location, two ports were presented, each associated with a distinct virtual context, requiring animals to select the correct port based on the current context. The trial ended when rats returned to the start location. Importantly, identical spatial locations and visual cues could correspond to different task phases depending on the start point, allowing us to dissociate positional coding from task-structural representations. During pre-learning sessions, only a single reward port was presented to eliminate choice, whereas post-learning sessions required context-dependent decisions and included greater variability in start positions. Throughout learning, we recorded single-unit activity and local field potentials from hippocampal CA1 and the subiculum simultaneously using tetrodes. Preliminary analyses revealed that a subset of subicular neurons encoded dynamic aspects of task structure. In pre-learning sessions, subicular activity was largely position-dependent; however, in post-learning sessions, a subset of neurons exhibited significant firing rate modulation across task phases. Using a theta-cycle-based field identification approach, we found that subicular place fields reorganized flexibly in response to changes in task structure. In contrast, although CA1 neurons also showed task-phase-dependent rate modulation, their place fields remained relatively stable

across different start locations within the same environment. Ongoing analyses aim to characterize how task-phase-specific representations emerge over the course of learning in the subiculum and to determine whether the development of flexible task-structure encoding is associated with improvements in behavioral performance.

Disclosures: S. Lee: None. **I. Lee:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.04/LL21

Topic: I.08. Learning and Memory

Support: Simons Foundation SFI-AN-NC-GB-Independence Postdoctoral-00006781 (S.M.L.)
SCGB NC-GB-CULM-00002730 (E.A.B)
WaNBRC P51OD010425
NINDS-UF1NS126485 (E.A.B)
NIA T32AG066574 (E.C.S.B.)
Schmidt Science Fellows in partnership with the Rhodes Trust (S.M.L.)

Title: High-density laminar recordings reveal layer-specific oscillatory dynamics in primate hippocampus

Authors: *M. J. JUTRAS[1,2], S. M. LANDI[1,2], E. BAKOTICH[1,2], E. A. BUFFALO[1,2]; [1]Neurobio. & Biophysics, Univ. of Washington, Seattle, WA; [2]Washington Natl. Biomed. Res. Ctr., Seattle, WA

Abstract: High density silicon probes spanning multiple hippocampal subregions offer an unprecedented opportunity to characterize layer-specific neural dynamics through simultaneous analysis of local field potentials (LFPs), current source density, and cross-frequency coupling. We conducted acute electrophysiological recordings using Neuropixels probes (NHP 1.0 Long) in the hippocampus of two behaving rhesus macaques during virtual navigation (5 sessions) and free-viewing (7 sessions) tasks. Recording locations were targeted via T1-weighted MRI, with probe advancement guided by hydraulic drive depth measurements and final placement determined by the presence of characteristic electrophysiological patterns, including extracellular action potentials. Probes were inserted vertically to traverse the full dorsal-ventral depth of the hippocampus, enabling concurrent recordings across dentate gyrus, CA3, and CA1.
Layer-specific analysis of hippocampal LFPs revealed characteristic patterns of oscillatory activity, phase-amplitude coupling, and current flow. Trial-averaged LFP analysis demonstrated layer-specific power spectral profiles, with theta-band (3-8 Hz) activity exhibiting a systematic phase progression across cell layers. Broadband oscillatory activity showed distinct spectral profiles across cell layers and subregions, with pronounced laminar variability in the theta-, beta-

(13-30 Hz) and gamma-frequency (30-120 Hz) bands. Current source density (CSD) analysis of laminar LFP recordings revealed a theta-band oscillation in transmembrane current flow concentrated in the region of the stratum lacunosum-moleculare (SLM), consistent with entorhinal cortical input patterns.
Cross-frequency coupling analysis revealed significant coupling (cluster-based permutation test, $p < 0.05$) between CSD phase (3-8 Hz) and LFP amplitude (20-120 Hz), with the strongest effects observed in CA3 and CA1 pyramidal layers. Interestingly, CA1 slow gamma-frequency oscillations (40-60 Hz) and fast gamma-frequency oscillations (60-120 Hz) were coupled to distinct phases of the low-frequency CSD.
These findings provide a high-resolution characterization of laminar dynamics spanning the dentate gyrus, CA3, and CA1 in a behaving primate. Simultaneous recording across these subregions opens new avenues for understanding how the hippocampal circuit integrates information across spatial and temporal scales during memory formation and retrieval.

Disclosures: M.J. Jutras: None. **S.M. Landi:** None. **E. Bakotich:** None. **E.A. Buffalo:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.05/LL22

Topic: I.08. Learning and Memory

Support: Schmidt Science Fellows in partnership with the Rhodes Trust (S.M.L.)
Simons Foundation SFI-AN-NC-GB-Independence Postdoctoral-00006781 (S.M.L.)
SCGB 542955 (E.A.B.)
SCGB NC-GB-CULM-00002730 (E.A.B)
WaNBRC P51OD010425
NIH-U19NS107609 (E.A.B., A.L.F., D.J.F.)
NINDS-UF1NS126485 (E.A.B, A.L.F.)

Title: Experience-dependent reorganization of hippocampal representations during VR learning

Authors: *S. M. LANDI[1,2,3], V. SHIRHATTI[4,5], D. J. FREEDMAN[4,5], A. L. FAIRHALL[3], E. A. BUFFALO[3,2];
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Abstract: The hippocampus encodes diverse task-related variables, yet how those representations evolve during learning remains unclear, particularly in primates where suitable paradigms and high-density recordings have been limited. Here, we recorded large hippocampal populations in two macaques as they learned naturalistic foraging tasks in virtual reality.

Monkeys used a joystick to navigate an open-field arena, harvesting rewards from visual targets whose values (high, medium, low) were determined either by position (Spatial task) or color (Color task). Because monkeys could collect only ~half the targets before each trial ended, foraging pressure drove rapid learning of novel value associations within a single session. This within-session learning, far faster than traditional paradigms, enabled real-time tracking of learning-related hippocampal dynamics. Neural activity was recorded with 32- and 64-channel Plexon S-probes and Neuropixels 1.0 NHP long probes along the hippocampal anterior-posterior axis (25 sessions, 1677 single units). Place cells and spatial view cells (significant Skaggs Information calculated with 1000 permutations, $p<0.001$) were rare overall but selectively enriched in the Spatial task (paired t-tests, $p<0.01$), though per-cell spatial information was comparable across tasks (Kolmogorov-Smirnov test, $p>0.1$). Most neurons were modulated by task and/or value during target approach, and as learning progressed, initially overlapping population activity patterns for different task-value combinations diverged into distinct representations. To test whether this representational differentiation tracked learning, we correlated trial-wise neural representational dissimilarity with behavioral rank value, a measure of how strongly monkeys prioritized higher-value targets. Across sessions, neural differentiation was positively coupled to behavioral value learning in both tasks (Wilcoxon signed-rank tests, $p<0.01$), and this coupling was task-dependent: the value boundaries driving it differed between the Spatial and Color tasks. These findings show that hippocampal value representations are rapidly reshaped by learning, differentiating within a single session as monkeys acquired new associations. Critically, this reorganization was flexible, with the structure of emerging representations tracking the task, reflecting whether value was defined spatially or by stimulus features.

Disclosures: S.M. Landi: None. **V. Shirhatti:** None. **D.J. Freedman:** None. **A.L. Fairhall:** None. **E.A. Buffalo:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.06/LL23

Topic: I.08. Learning and Memory

Support: SCGB NC-GB-CULM-00002730 (E.A.B)
WaNBRC P51OD010425
NINDS-UF1NS126485 (E.A.B, A.L.F.)
NIMH-R01MH132171 (M.W.H., E.A.B.)
NIA T32AG066574

Title: Hippocampal population activity reinstates an image-specific code during naturalistic free-viewing in macaques

Authors: *E. BAKOTICH[1,2,3,4], E. A. BUFFALO[2,4];
[2]Neurobio. and Biophysics, [3]Grad. Program in Neurosci., [1]Univ. of Washington, Seattle, WA;
[4]Washington Natl. Biomed. Res. Ctr., Seattle, WA

Abstract: The hippocampus is thought to support memory for individual experiences by representing each event with a distinct population signature that is reinstated upon re-encounter. Whether primate hippocampal populations carry such experience-specific signatures remains unknown. We recorded single-unit activity from the hippocampus using Neuropixels probes in two rhesus macaques (6 sessions, 93-206 sorted units/session) engaged in free exploration of visual images. In 6-9 blocks per session, monkeys viewed 16 novel images followed by repeat presentations of the same images, with reward delivered on interleaved eye-calibration trials. For each novel/repeat pair of the same image, we computed population vectors of neural activity during fixations and quantified their similarity via a sign-aware Jaccard concordance over per-unit enhanced and suppressed states. Population vectors for same-image pairs showed significantly higher concordance than cross-image pairs in all sessions with both jointly-enhanced and jointly-suppressed units contributing (Mann-Whitney U $p<10^{-20}$). The effect held on Pearson correlation of continuous rate vectors and produced consistent results across all sessions (matched > cross-image, Mann-Whitney U $p<10^{-10}$). Novelty-modulated, repeat-modulated, and non-selective units all contributed to the same-image effect across all sessions, indicating a population code for image identity dissociable from novelty signals. We performed three analyses to assess the impact of bottom-up visual drive and task state. First, cross-image visual feature similarity (ResNet50 cosine) explained <0.5% of the variance in cross-image neural similarity ($|\text{Spearman } \rho| \leq 0.07$). Second, the same-image concordance was ~10× larger than between cross-image fixations from the same novel/repeat condition in all sessions, indicating that image identity, rather than novelty state, drives the effect. Third, within trials, neural concordance for fixation pairs sampling different image regions was similar to that for same-region pairs, indicating that gaze position contributed little to population-vector similarity. These results suggest that primate hippocampal populations carry a content-specific, largely gaze- and feature-invariant code for individual images, reinstated across separate encounters during naturalistic viewing. Because this code is specific to image identity yet independent of novelty state, it signals which experience is recurring rather than generic familiarity, consistent with an index-like code for individual items or events.

Disclosures: E. Bakotich: None. **E.A. Buffalo:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.07/LL24

Topic: I.08. Learning and Memory

Support: NIMH R01MH114961 (to AMP)

Title: Neonatal Ovariectomy-Enhancement of Fear Learning and Its Relationship to Perineuronal Nets (PNNs) and GABA-A receptor α4 subunit Expression in the Dorsal Hippocampus

Authors: *I. GUPTA[1], L. M. COLON[2], A. M. POULOS[3];
[1]Univ. of Albany, Albany, NY; [2]Neurosci., Children's Hosp. of Philadelphia, Philadelphia, PA; [3]Dept. of Psychology, Univ. At Albany, SUNY, Albany, NY

Abstract: Gonadal hormones, such as estrogens, can have organizational effects on the neural circuitry underlying context fear learning in a sex-specific manner. In female rats, estradiol concentration rises in the hours following birth, peaking about 2 weeks postnatally, then remains low until pubertal onset. We previously showed that neonatal (P0), but not prepubertal (P28), ovariectomy enhances fear learning in adulthood (Colón et al., 2023),suggesting gonadal hormones present during the neonatal period play an organizational role in the development of fear-learning circuitry. Two critical modulators of excitability, plasticity, learning, and memory are perineuronal nets (PNNs) and the GABA-A receptoralpha-4 (α4) subunit; both are sensitive to changes in gonadal hormone levels. Newborn female Long Evans pups (P0) underwent ovariectomy (n=3) or sham surgery (n=3)and were later sacrificed and perfused as adults. Coronal brain sections of the dorsal hippocampus were processed for Nissl staining and IHC for PNNs and α4. Nissl-stained sections will be used to delineate the anterior-posterior positions of each section, specifically regions such as the Cornu Ammonis (CA) fields, strata, and the dentate gyrus. Preliminary findings in gonadally intact rats demonstrate consistent staining for both PNNs and α4, with notable expression throughout the pyramidal layers of CA3 and CA2. Preliminary findings in ovariectomized rats also demonstrate consistent staining for PNNs and α4 in pyramidal layers of CA3 and CA2, as well as CA1 and within the dentate gyrus.

Disclosures: I. Gupta: None. **L.M. Colon:** None. **A.M. Poulos:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.08/LL25

Topic: I.08. Learning and Memory

Support: Bender Scientific Fund (to AMP)

Title: Connectivity and molecular organization across hippocampal-entorhinal regions

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Abstract: The hippocampal formation and entorhinal cortex support contextual memory and long-term retrieval by integrating hippocampal computations with cortical contextual and multimodal inputs. CA3 is a key hub for pattern completion, but how CA3-centered anatomical

connectivity aligns with molecular identity across dentate gyrus, CA1/subiculum, and entorhinal subdivisions remains incompletely integrated across public atlas datasets. We performed an exploratory atlas-based analysis integrating Allen Mouse Brain Connectivity Atlas projection data with cell-level and spatial transcriptomic datasets across hippocampal-entorhinal regions. Representative Allen anterograde tracer experiments were selected for DG, CA3, CA1, ENTm, and ENTl source regions. Structure-unionized projection-density and projection-volume values were extracted for DG, CA3, CA1, SUB, ProS, ENTm, and ENTl targets, organized into source-by-target matrices, and row-normalized within each source experiment to compare relative target-distribution patterns rather than absolute projection strength. To examine molecular organization, we analyzed a curated 58-gene expression table across DG, CA3, CA1-ProS, L2 IT ENTl, L2 IT ENTm, and L3 IT ENT. Candidate genes were grouped into excitability, synaptic signaling, activity-dependent plasticity, and regional-identity categories. UMAP, hierarchical clustering, gene-wise z-score heatmaps, enrichment/specificity scores, and gene-program scoring were used to compare subclass-level molecular patterns. ABCA MERFISH spatial transcriptomic data were used to visualize spatial expression and co-expression of selected overlapping marker genes. Row-normalized Allen matrices revealed region-specific hippocampal-entorhinal projection patterns. Entorhinal sources showed broader relative projection density and volume across selected targets, whereas CA3 showed a more restricted normalized projection profile. Molecular analyses separated hippocampal and entorhinal subclasses and identified CA3-associated relative enrichment of excitability, synaptic signaling, plasticity, and hippocampal/subfield identity signatures, while entorhinal subclasses showed stronger layer- and region-associated signatures. Spatial visualization supported regionally organized marker expression and co-expression across hippocampal-entorhinal tissue space. Together, these exploratory findings identify coordinated anatomical and molecular organization across hippocampal-entorhinal regions and point to CA3 as a molecularly distinct node relevant to contextual memory circuitry.

Disclosures: Z. Taherizadeh Zarandi: None. **A.M. Poulos:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.09/LL26

Topic: I.08. Learning and Memory

Title: Muscle-Derived Small Extracellular Vesicles Mediate Exercise-Induced Cognitive Protection in Chronic Cerebral Hypoperfusion

Authors: *H. LIN;
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Abstract: Physical exercise protects against cognitive impairment caused by chronic cerebral hypoperfusion (CCH). However, the mechanisms through which exercise sends signals from the

periphery to the central nervous system remain incompletely understood. This study demonstrated that exercise promotes the secretion of muscle-derived small extracellular vesicles (sEVs), which facilitate interorgan communication between the muscle and the brain. Systematic delivery of muscle-derived sEVs enhances synaptic plasticity and alleviated cognitive impairment in CCH. Notably, miRNA sequencing reveal miR-17/20a-5p as key cargos in sEVs involved in the exercise-induced muscle-brain crosstalk. Muscle-derived sEVs are also identified as the primary source of swimming-induced miR-17/20a-5p in circulating sEVs. Mechanistically, miR-17/20a-5p binds to the DEP-domain containing mTOR-interacting protein (DEPTOR) and activates the mammalian target of rapamycin (mTOR) pathway in the hippocampus. Depletion of miR-17/20a-5p from muscle-derived sEVs impairs the exercise-induced enhancement of synaptic plasticity and cognitive function. Moreover, overexpression of DEPTOR in the hippocampus attenuates the cognitive benefits of exercise. Conversely, hippocampus-specific activation of mTOR reverses these effects, highlighting the crucial role of mTOR in mediating the positive effects of exercise. Collectively, these findings identify miR-17/20a-5p in muscle-derived sEVs as the exercise-induced myokine with potent effects on the brain, emphasizing the therapeutic potential of exercise in managing cognitive impairment.

Disclosures: H. Lin: None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.10/LL27

Topic: I.08. Learning and Memory

Support: K01AG054729
P20GM113131
R15MH126317
R15MH125305

Title: Disruption of "Primed-Silent" Neural Activity Hierarchy via NMDA Receptor Blockade: An in vivo Calcium, Fos imaging, and EEG Waveform Analysis on the Hippocampus

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Abstract: It is established that a subset of “primed” neurons with elevated excitability in memory-related brain regions is preferentially recruited to engage in learning and associative memory formation. However, to date, little is known about how such a “primed-silent” neural activity hierarchy is established and maintained. Our computational model suggests that non-linear NMDAR-mediated synaptic conductance is essential for the formation and maintenance of this hierarchy. Leveraging *in vivo* hippocampal calcium imaging, Fos-GFP imaging, and

hippocampal EEG recording on freely behaving mice, we tested the hypothesis that the neural activity hierarchy in the hippocampus is disrupted by NMDAR blockade using ketamine or MK801. We show that under baseline conditions, a small portion of neurons consistently maintained high activity ranks and displayed synchronized calcium dynamics during learning, whereas most neurons remained weakly active. Ketamine induced NMDAR blockade increased the instability of neuronal activity rankings across the hippocampal network, and redistribution of ranks occurred across the neuronal population observed in both calcium and Fos imaging. Hippocampal EEG recordings under NMDA blockade revealed a disrupted neuronal activity hierarchy, evidenced by hyper-synchronization. Together, these results suggest that associative memory depends on a stable activity hierarchy among hippocampal neurons. Disruption of the hierarchy may implicate in cognitive dysfunction and psychosis-related disorders associated with NMDAR hypofunction.

Disclosures: L. Wang: None. **Y. Zhou:** None. **L. Qiu:** None. **M. Lyon:** None. **X. Chen:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.11/LL28

Topic: I.08. Learning and Memory

Title: Neural correlates of memory strength in the primate hippocampus

Authors: *A. PICCATO[1], M. G. POTTA[1], A. SOLTANI[2], M. JAZAYERI[3];
[1]MIT, Cambridge, MA; [2]Psychological and Brain Sci., Dartmouth Univ., Hanover, NH; [3]Brain and Cognitive Sci., Massachusetts Inst. of Technol. Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: A hallmark of long-term memory is its dependence on experience: recently and repeatedly encountered associations are retrieved faster and more accurately than remote or infrequent ones. Yet the neural and computational principles governing how memory strength accumulates and decays are not known. We designed a visuo-spatial association task in which subjects form lasting image-location associations over tens of trials.To characterize the trial-by-trial dynamics of learning and forgetting, we developed latent-variable models in which the memory strength of each image-location association evolved through two interacting processes: decay over elapsed time and updating upon image exposure. Behavioral analyses across model variants revealed that decay was state-dependent: stronger memories decayed more slowly. Equivalent synaptic learning models showed that this form of state-dependent decay naturally arises from metaplasticity, whereby stronger synapses become more resistant to change, producing hysteresis in learning.To identify neural correlates of these dynamics, we recorded population activity from CA1 and CA3 in two trained macaques using Neuropixels probes, yielding 3,698 units. We found substantial spatial and visual tuning, with approximately 27% and 16% of units showing significant selectivity, respectively. Model-inferred memory strength

modulated the activity of spatially selective hippocampal neurons in two complementary ways. First, firing-rate changes showed a structured relationship to memory strength consistent with spatial sharpening: responses increased at a neuron's preferred location and decreased at non-preferred locations. Second, trial-to-trial response variability of spatially selective cells decreased with memory strength. Together, these findings show that mnemonic strength follows state-dependent dynamics in the primate brain and identify two complementary hippocampal signatures of associative learning: sharpening of spatial tuning and increased reliability of spatial responses.

Disclosures: A. Piccato: None. **M.G. Potta:** None. **A. Soltani:** None. **M. Jazayeri:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.12/LL29

Topic: I.08. Learning and Memory

Support: NIH R00NS127815-04
NIH T32GM158468-01
Klingenstein Philanthropies
Whitehall Foundation

Title: Dendritic calcium store dynamics during navigational learning

Authors: *I. HUA[1], J. O'HARE[1,2];
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Abstract: Learning begins when experience drives increased neuronal activity, triggering Ca^{2+}-dependent signaling pathways that strengthen or weaken synaptic connections between neurons. Recent work identified a novel form of synaptic plasticity, behavioral timescale synaptic plasticity (BTSP), that is sufficient to drive rapid, single-trial formation of new place fields in hippocampal neurons. According to BTSP, a Ca^{2+}-dependent plateau potential in a pyramidal neuron's dendrites strengthens synapses receiving excitatory input within several seconds of plateau initiation. Single-shot learning over longer, non-Hebbian timescales may help explain how the brain links events across time to form ethologically relevant associations. However, the molecular mechanisms that extend a relatively brief plateau potential's influence into a temporal window an order of magnitude longer are unknown.
We propose that the endoplasmic reticulum (ER) bridges this gap. The ER pervades the entire dendritic arbor, where it acts as a dynamic intracellular Ca^{2+} store capable of activity-dependent Ca^{2+} release. Recent lines of evidence suggest that this intracellular Ca^{2+} release is engaged during BTSP, raising the possibility that the ER may regulate synaptic plasticity *in vivo* by shaping the spatiotemporal patterning of cytosolic Ca^{2+} during the induction phase.
Here, we simultaneously monitored somatic and dendritic ER and cytosolic Ca^{2+} signals from

CA1 pyramidal neurons using dual-color, volumetric two-photon microscopy and single-cell DNA electroporation. We leveraged a virtual reality-based navigational learning paradigm to promote spontaneous place field formation. This approach enabled us to reliably monitor subcellular Ca^{2+} signals at the precise moment of place field formation in behaving animals, despite imaging 1-3 neurons at a time. By comprehensively profiling dendritic ER Ca^{2+} dynamics as they relate to cytosolic transients, animal behavior, and place field formation, we provide the first insights into how dendritic Ca^{2+} stores shape behavioral and neural correlates of learning in behaving mice.

Disclosures: I. Hua: None. **J. O'Hare:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.13/LL30

Topic: I.08. Learning and Memory

Support: Klingenstein-Simons Fellowship
Whitehall Foundation

Title: All-optical physiology reveals an inhibitory synaptic control of behavioral timescale plasticity

Authors: *K. SWIFT[1], X. CHEN[2], K. WEN[2], E. WONG[2], A. Q. KASHAY[2], I. R. FIETE[3], Y. LI[5], L. Z. FAN[4];
[1]MIT, Cambridge, MA; [2]MIT, Boston, MA; [3]Ctr. for Learning and Memory, [4]Brain and Cognitive Sci., MIT, Cambridge, MA; [5]Sch. of life sciences, Peking Univ., Beijing, China

Abstract: Learning and memory involve plastic changes in synaptic strength and circuit dynamics, yet the precise synaptic mechanisms encoding behaviorally relevant information in behaving mammals have remained largely unclear. In the hippocampus, while rapid place field formation is thought to emerge through excitatory synaptic plasticity, how inhibitory synaptic plasticity controls this process remains unknown. Here, we combined genetically encoded voltage imaging with targeted optogenetic activation and silencing of pre- and post-synaptic neurons to investigate inhibitory synaptic plasticity during spatial navigation. Simultaneous optogenetic activation of CA1 pyramidal neurons and elicitation of inhibitory postsynaptic potentials (IPSPs) revealed that CA1 plateau potentials trigger a transient endocannabinoid-mediated suppression of inhibitory synaptic inputs on a timescale of seconds. Furthermore, this suppression of inhibition is required for the rapid emergence of place fields. These results reveal rapid, activity-dependent inhibitory synaptic plasticity in vivo and establish an inhibitory synaptic mechanism controlling behavioral timescale plasticity in behaving mammals.

Disclosures: K. Swift: None. **X. Chen:** None. **K. Wen:** None. **E. Wong:** None. **A.Q. Kashay:** None. **I.R. Fiete:** None. **Y. Li:** None. **L.Z. Fan:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.14/LL31

Topic: I.08. Learning and Memory

Title: Hippocampal ensemble encoding of continuous visual episodes in freely viewing primates

Authors: *J. PIMIENTO CAICEDO[1], S. VIJAYRAGHAVAN[2], J. C. MARTINEZ-TRUJILLO[3];
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Abstract: Many episodic memories arise from spatiotemporal visual experiences shaped by our interactions with the world. Although neurons in visual cortices encode individual elements of these experiences, it remains unclear how they are transformed into episodic memories. In non-human primates, converging evidence suggests that the hippocampus is especially responsive to visual input: it is strongly interconnected with inferior temporal cortex and area V4, contributes to scene recognition, shapes memory-related gaze patterns, modulates visual attention during encoding, and contains view cells tuned to specific visual features. Yet it remains unknown whether and how hippocampal ensembles encode extended visual episodes composed of sequential scenes, such as movies. To address this question, we developed a free-viewing movie paradigm in common marmosets, simultaneously recording eye position (Eyelink 1000) and neural activity in hippocampal area CA3 using high-density Neuropixels probes. Gaze patterns during movie viewing were highly systematic: strongly correlated across repeated presentations of the same movie and markedly less correlated across different movies. These differences reflected movie content, as gaze reliably tracked salient features such as faces, moving characters, and other behaviorally relevant elements of the scene. Correspondingly, hippocampal neurons (average >100 simultaneously recorded units per session; 5 sessions analyzed) showed robust modulation during movie presentation, including both increases and decreases in firing rate at specific segments within individual movies. Notably, some of these response patterns remained stable after delays exceeding 10 minutes, suggesting a degree of persistence consistent with episodic memory encoding. At the population level, a linear support vector machine trained on ensemble activity could reliably classify movie identity (80% accuracy; chance: 33%; $p < 0.001$), demonstrating that hippocampal population codes contain sufficient information to distinguish among continuous visual episodes. Together, these findings support the view that the primate hippocampus encodes continuous visual experiences as structured spatiotemporal episodes. The presence of stable, segment-specific responses after long delays further suggests a potential neural substrate through which such experiences may be encoded, maintained, and later retrieved as episodic memories.

Disclosures: J. Pimiento Caicedo: None. **S. Vijayraghavan:** None. **J.C. Martinez-Trujillo:** None.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.15/LL32

Topic: I.08. Learning and Memory

Support: Packard Foundation
NIH Grant R01 NS109226
NIH Grant 2RF1 NS109226
NIH Grant RF1 AG078736-01
McCamish Foundation
Friends and Alumni of Georgia Tech
The Lane Family
NIH Grant 5F31AG066410
NIH Grant T32 NS007480-18
Fulton County Elder Health Science Fellowship
Wright Family
J. Norman and Rosalyn Wells Fellowship
NSF GRFP grant DGE-1444932
NIH grant T32NS096050-22
Emory University Women's Club Graduate Research Fellowship

Title: New Information Triggers PV-Related Reorganization of Hippocampal Representations

Authors: *S. D. CUSHING[1], A. L. PAULSON[2], S. M. PRINCE[3], N. JEONG[4], A. C. SINGER[5]; [1]Georgia Inst. of Technol., Atlanta, GA; [2]Georgia Inst. of Technol., Cary, NC; [3]Lawrence Berkeley Natl. Lab., Berkeley, CA; [4]Emory Univ. & Georgia Tech., Atlanta, GA; [5]Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. & Emory Univ., Atlanta, GA

Abstract: Navigating in a dynamic world requires flexibly redirecting as goal locations change. However, the neural mechanisms that rapidly update internal representations when new information changes navigation plans remain unclear because most navigation studies use static environments. Thus, we developed a navigation task that precisely introduces "pivotal" new information using virtual reality (VR), combined with large-scale neural recordings, to investigate neural reorganization underlying flexible navigation when goal locations change. Using this task, we previously showed that pivotal new information that requires a change in navigation plans rapidly increases non-local representations of reward locations in CA1 (Prince et al, 2025). Here we show that pivotal environmental changes trigger a drastic decrease in firing of CA1 excitatory cells that represent current position, or "local" cells, in contrast to trials without new pivotal information and in contrast to static environments. Mice were trained to complete a y-maze, where an initial cue indicated the rewarded arm and animals had to maintain that information over a delay. In a subset of "switch" trials, a second "update" cue appeared during the delay indicating that a different arm would be rewarded. On switch trials, but not

delay-only trials, firing of local cells significantly decreased following the update cue. This decrease in local cell activity coincided with an increase in PV interneuron firing, suggesting that inhibitory cells suppress outdated spatial representations. Interestingly, not all pyramidal cell activity was suppressed: the firing of pyramidal cells that represented goal arms increased. We then determined if optogenetic stimulation of PV+ interneurons was sufficient to cause this decrease in local pyramidal place cell firing in static environments using two prior data sets. Finally, we assessed gamma activity in CA1 during the update cue to determine if entorhinal cortex or CA3 inputs are correlated with increases in representations of reward locations. These results show that new pivotal information triggers rapid increases in PV activity, suppression of local spatial information, and increases in goal representations. These findings suggest that new information triggers a rapid transition from representing the current position to representing future goals, and PV interneurons facilitate that transition by suppressing outdated local representations.

Disclosures: S.D. Cushing: None. **A.L. Paulson:** None. **S.M. Prince:** None. **N. Jeong:** None. **A.C. Singer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owns stock in Cognito Therapeutics.

Poster

PSTR247: Hippocampal Circuit III

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR247.16/LL33

Topic: I.08. Learning and Memory

Support: NIH grant MH135565

Title: Cholinergic and circuit effects on engram formation, stabilization and activation

Authors: Z. HAN[1], V. BOOTH[3], *M. R. ZOCHOWSKI[2];
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Abstract: Animals and humans are barraged by external stimuli throughout their lives. Many of those events are stored in the brain in real time and later consolidated to form long-term memories. While creation and stabilization of network wide neuronal representations, so called memory engrams, are known to underlie memory formation it is not clear how these representations are rapidly formed, consolidated and later retrieved through network spiking activity patterns. Here we investigated in silico how neuromodulatory effects of cholinergic activation (modeled via M1 muscarinic receptor activation), as experienced during different activity states such as active waking, quiet waking, REM and/or NREM sleep, together with underlying network structure can optimize and facilitate formation and stabilization of memory engrams in hippocampal CA3-type networks. Specifically, we built interacting excitatory/inhibitory networks, composed of biophysical neuronal models based on the Hodgkin-

Huxley formalism to investigate optimal circuit properties and network wide activity correlates underlying engram formation and stabilization under different levels of cholinergic modulation. We specifically identified optimal network topologies and corresponding dynamical regimes that promote storage of multiple representations of interacting but separate memory engrams. We found that, depending on network connectivity structure and acetylcholine levels, developing engrams may merge with previously existing ones or form competing memory representations. Furthermore, we found that changes in cholinergic modulation promote a transition from frequency-based coding, for high ACh levels during wake and REM sleep, to synchrony based coding and formation of ripple-like events for low ACh levels during quite waking and sleep. The ripple-like events act to consolidate engram structure for individual memories and at the same time separate unrelated representations.In all, our results shed light on the cholinergic and network effects underlying dynamics of formation and stabilization of multiple engrams in the network.

Disclosures: Z. Han: None. **V. Booth:** None. **M.R. Zochowski:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.01/LL34

Topic: I.09. Spatial Navigation

Title: The zebrafish entopeduncular nucleus-to-ventral habenula pathway facilitates a local-to-global mapping strategy for navigation within a complex environment

Authors: *C. S. PENARANDA[1], J. S. KANWAL[2];
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Abstract: To navigate complex environments, animals must employ stable behavioral strategies to create a neural representation or map of space. To test whether map creation follows integration of randomly sampled spatial chunks or systematic local-to-global stitching, we placed adult wild-type zebrafish (Danio rerio) in a circular arena divided into six inner radial sectors connected by an outer corridor. In a darkroom, infrared imaging continuously tracked head position using ZebraZoom. Zebrafish of both sexes (6-12 months; n=20) underwent 20-min free exploration. Tracking yielded sequential sector-entry transitions. Adjacent-zone transitions occurred more often than chance (42% observed vs 33% expected). A “global repeat” (GR) was counted when animals returned to the same zone via the outer corridor after circumventing all other sectors; this occurred less often than chance (10% vs 17%). First-order Markov analyses revealed bout-like persistence of adjacent and non-adjacent exploration states. GR analyses showed that fish frequently sampled multiple novel zones before returning to visited zones. We next asked whether this organization could be shaped into persistent goal-directed behavior and whether the entopeduncular nucleus-to-ventral habenula (EPN-vHb) pathway contributes to stabilization. 5-month-old y471 transgenic (BGi-epNTR-TagRFP) zebrafish were trained to

complete progressively stricter GR trajectories for social reward in a forced-choice paradigm. Controls reached criterion after 12 rewarded GRs. To establish the role of the EPN-vHb circuit, transgenics (n=10) were exposed to 10 mM metronidazole (MTZ) for 24 h to induce ablation; untreated transgenics served as controls (n=8). Both groups acquired rewarded GR behavior (80% ablated; 88% control); ablated fish completed early low-stringency stages significantly faster (Welch's two-sample t-tests, $p<0.05$) but became more variable under stricter criteria. During a 10-min unrewarded probe after barrier removal, significantly fewer ablated fish expressed at least one perfect GR than controls (10%, 1/10 vs 62%, 5/8; Fisher's exact test, $p=0.043$). Ablated fish also made more inner-zone entries (Welch's two-sample t-test, $p<0.01$) and showed a stronger adjacency bias (68.4% vs 50.6%; Welch's two-sample t-test, $p<0.05$), suggesting reversion toward local exploration rather than reduced engagement. Analyses were unblinded; each fish was an independent experimental unit. Sex differences were not assessed. Together, these findings implicate the EPN-vHb pathway in sustaining attention to integrate sensorimotor information needed to map complex environments within neural space.

Disclosures: C.S. Penaranda: None. **J.S. Kanwal:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.02/LL35

Topic: I.09. Spatial Navigation

Support: ISF 0501/25

Title: Large Scale Laboratory Visual Navigation in Flowerhorn Cichlids 101: From Rigorous Methodology to Complex Target-Finding Behavior

Authors: *N. GUR[1], A. LAZAROVICH[2], O. BEN-SHAHAR[3];
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Abstract: Large Scale Laboratory Visual Navigation in Flowerhorn Cichlids 101: From Rigorous Methodology to Complex Target-Finding Behavior Understanding whether teleost fish form and use internal spatial representations requires experimental paradigms of sufficient size, rigor, and complexity to distinguish genuine navigational skills from simple stimulus-response reactive behavior. We developed a large, remotely controlled, integrated experimental environment that runs mostly autonomously and based on a Fish-Operated Mobile Aquarium (FOMA) — a wheeled water tank that translates a fish's position within the tank into directional movement of the vehicle — and used it to study navigation in flowerhorn cichlids in a 5×5 m terrestrial arena, two order of magnitude larger than subjects' size. Fish were trained to use the FOMA to approach a red circular target mounted on the arena walls, rewarded with food upon success, and tested across a series of progressively demanding navigational conditions.Five fish

were analyzed across 7-9 training sessions each (approximately 50-80 trials per individual). All successfully acquired FOMA control, with individual target-reach success rates of 76-97%. Across the group, vehicle path length decreased, and path linearity increased over trials, reflecting progressively more direct navigation toward the target. On average, swimming speed and heading variability both declined across trials, indicating increasingly efficient and directed motor control within the aquarium. Between-session performance retention was observed in four of five fish.Building on this baseline, fish were tested under systematically counterbalanced target wall conditions, as well as varying launch sites different than the training conditions, to assess spatial asymmetries in navigation performance. Fish were subsequently tested in various target-distractor configurations, in which the rewarded target and an unrewarded distractor were simultaneously present, requiring selective navigation toward the correct visual cue.The collective results in all these experiments demonstrate that flowerhorn cichlids are not only able to learn FOMA control, and visual navigation skills, but are capable of flexible, cue-selective spatial behavior under increasingly complex conditions. Moreover, by further exploitation of the presented experimental environment and apparatus for more complex conditions in the future, this exploratory study establishes a scalable platform for probing the richness of spatial representation in the teleost brain.

Disclosures: N. Gur: None. **A. Lazarovich:** None. **O. Ben-Shahar:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.03/LL36

Topic: I.09. Spatial Navigation

Title: Modeling cue-to-task efficiency during goal-directed spatial navigation in adult zebrafish, Danio rerio

Authors: *E. L. MANSON[1], J. S. KANWAL[2];
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Abstract: Spatial navigation within a two-dimensional plane is simply a series of timely, cue- or memory-driven left- or right-turn decisions. These decisions require attention to allothetic cues and idiothetic sensorimotor feedback as well as a working memory for goal-directed tasks that may be critical for survival, for example, during homing or foraging. We devised a working memory paradigm to track cue-to-execution efficiency in an adult zebrafish, *Danio rerio*, as a model of Parkinson's disease for action selection and multiple sclerosis for signal processing/conduction speed. Fish (n = 6) initiated experimental trials by swimming to the home zone in a small (6.60 x 20.70 cm) tank enclosed in a dark chamber (Zantiks LT system). A white bar (6.60 x 1.25 cm) and dark grey square (6.60 x 6.60) marked the "home zone." Entering the home zone turned on an overhead light, which signaled trial initiation. Entering the adjacent "trigger zone" turned off the overhead light and projected the visual reference cue, a cyan-filled

circle (diameter 1.5 cm), underwater (randomly left or right) via a right-angle optical prism. Exiting the trigger zone turned off the reference cue and initiated the response window countdown. A swim within the response window (successively reduced from 10 to 6 s) contralateral to the cue side (Go) resulted in a social reward (view of zebrafish) whereas a swim to the side ipsilateral to the cue provided no reward. Go trials were marked as "pass" and all other trials were marked as "fail." Two consecutive passes reduced the response-window by 1 s. Three consecutive passes at 4 s marked the end of the experiment. Control group fish (n = 6) were subjected to an identical paradigm except there was no reward displayed when the fish swam contralateral to the reference cue location. Fish learned to predict and navigate to the reward side in 44.35 ± 7.23 minutes (n=4) and accomplished the task twice successively down to 6 s. There was a decrease in latency across the experimental group as trials progressed. Two fish failed to learn the task. Our data suggest that adult zebrafish can process and perform an imagined spatial navigation task within a 6 s attentional window.

Disclosures: E.L. Manson: None. **J.S. Kanwal:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.04/LL37

Topic: I.09. Spatial Navigation

Title: Associative learning in adult transparent glassfish, Danionella priapus

Authors: *A. STUART[1,2], A. RAVAN[3], C. MORROW[3], V. JAYARAMAN[1];
[1]Janelia Res. Campus, HHMI, Ashburn, VA; [2]Neurosci., Johns Hopkins Univ., Baltimore, MD;
[3]HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Species from insects to mammals have demonstrated associative learning in tasks ranging in complexity from Pavlovian stimulus-response pairing to cognitively challenging integration of spatially and temporally dispersed cues. Associative learning, particularly during complex tasks, is likely a brainwide process. However, the scope of previous work has typically been restricted to one or a few brain regions due to experimental constraints. To overcome these limitations and move toward a brainwide account of the mechanisms of associative learning, we use a new model organism, the transparent glassfish *Danionella priapus*, a relative of zebrafish (*Danio rerio*). *Danionella* retain larval-like transparency in adulthood, enabling optical access to its small brain (1-2 mm^3) throughout its lifespan. While larval zebrafish have difficulty with associative learning paradigms, we show adult *Danionella* can be taught to associate colors, patterns, or sounds with the future location of a reward within a y-maze. In contrast with earlier fish training paradigms, where fish received reward after swimming toward the conditioned stimulus, we show *Danionella* learn non-directional cues, using the information received at one location to inform turning direction at the choice point of the y-maze without an explicit signal at the eventual reward location. Development of these new behavioral paradigms in a transparent

adult animal is a foundational step toward understanding how brainwide activity underlies complex cognitive tasks across levels of neural computation from sensory input and internal representation of goal locations, to motor output.

Disclosures: A. Stuart: None. **A. Ravan:** None. **C. Morrow:** None. **V. Jayaraman:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.05/LL38

Topic: I.09. Spatial Navigation

Support: Howard Hughes Medical Institute
NIH Grant U19NS104653
Simons Collaboration on the Global Brain Grant SCGB542943SPI

Title: A whole-brain larval zebrafish connectome reveals pathways underlying heading representation and self-motion integration

Authors: L. TAO[1], X. LIU[1], S.-Y. TAKEMURA[1], B. HULSE[1], A. B.-Y. CHEN[2], M. PETKOVA[2], N. IYER[1], R. SCHALEK[2], C. KNECHT[2], S. BERG[1], W. KORFF[1], G. W. MEISSNER[1], M. JANUSZEWSKI[3], J.-M. LUECKMANN[3], V. JAIN[4], J. W. LICHTMAN[2], F. ENGERT[2], A. M. HERMUNDSTAD[1], V. JAYARAMAN[1], R. PORTUGUES[5], *S. ROMANI[1], M. B. AHRENS[1];
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Abstract: Appropriate directional movement requires integrating sensory inputs and motor efference signals to maintain an accurate representation of heading relative to a goal. Although many vertebrate studies have identified neurons that encode heading, landmarks, and self-motion cues, the synaptic pathways through which these signals converge to update internal heading representations remain unknown. In larval zebrafish, anterior hindbrain neurons with neurites in the interpeduncular nucleus (IPN) integrate past swimming movements to maintain an internal representation of angular position relative to landmark anchors provided by the left habenula. However, the circuit mechanisms supporting this computation and the extent to which additional sensory and vestibular signals contribute remain unknown. Here, we leverage a community-generated whole-brain larval zebrafish structure-function dataset, in which whole-brain neuronal activity was recorded before reconstruction of the same animal's connectome, to identify the pathways conveying landmark, optic flow, water flow, vestibular yaw, and motor efference signals to the dorsal IPN. We reveal connectivity motifs consistent with self-motion integration and propose a circuit mechanism by which heading representations are updated during navigation. Together, these results identify candidate circuit mechanisms through which sensory

and motor signals are integrated to compute and update internal heading representations that can guide navigational behaviors.

Disclosures: L. Tao: None. **X. Liu:** None. **S. Takemura:** None. **B. Hulse:** None. **A.B. Chen:** None. **M. Petkova:** None. **N. Iyer:** None. **R. Schalek:** None. **C. Knecht:** None. **S. Berg:** None. **W. Korff:** None. **G.W. Meissner:** None. **M. Januszewski:** None. **J. Lueckmann:** None. **V. Jain:** None. **J.W. Lichtman:** None. **F. Engert:** None. **A.M. Hermundstad:** None. **V. Jayaraman:** None. **R. Portugues:** None. **S. Romani:** None. **M.B. Ahrens:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.06/LL39

Topic: I.09. Spatial Navigation

Support: Jane Coffin Childs
Howard Hughes Medical Intitute
NIH DP2NS132373
NSF 2318081
Shurl and Kay Curci Foundation
Seed Grant from the Brain Research Foundation
Alfred P. Sloan Fellowship
Biohub, San Francisco

Title: Octopamine instructs head direction plasticity

Authors: *M. H. PLITT[1], D. B. TURNER-EVANS[3], A. LAYDEN[4], V. JAYARAMAN[5], Y. E. FISHER[2];
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Abstract: Many plasticity rules rely on adjusting the strength of synapses between pairs of cells based on their coincident activity. We uncovered a new mechanism for coincidence detection in the Drosophila head direction network. To maintain an accurate sense of direction, head direction neurons that signal orientation during navigation must learn to anchor to relevant external sensory cues in novel environments. Yet the synaptic mechanism for this form of unsupervised learning is unknown in any organism. In Drosophila, GABAergic visual inputs converge onto head direction neurons, and these inhibitory synapses change strength with experience to learn the relationship between visual landmarks and head direction. However, how coincident pre- and postsynaptic activity is detected across this inhibitory synapse is not understood. We discovered that neurons which release the monoamine octopamine close a feedback loop that conveys postsynaptic head direction activity onto presynaptic terminals of

visual inputs. This octopamine pathway is required for anchoring the head direction network to visual cues. Furthermore, pairing structured activation of octopamine neurons with a visual cue is sufficient to drive rapid plasticity, even without postsynaptic head direction cell activity. Previous work has extensively characterized coincidence detection mechanisms at excitatory synapses; our work defines a novel mechanism for coincidence detection at an inhibitory synapse, in which postsynaptic activity is relayed via a neuromodulatory neuron onto presynaptic terminals.

Disclosures: M.H. Plitt: None. **D.B. Turner-Evans:** None. **A. Layden:** None. **V. Jayaraman:** None. **Y.E. Fisher:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.07/LL40

Topic: I.09. Spatial Navigation

Support: NIH R01 NS129647
HHMI

Title: A paradigm for studying flexible navigation in Drosophila

Authors: *B. S. MOITT[1], W. ZHANG[2], N. L. PETTIT[2], R. I. WILSON[2,3];
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Abstract: Goal directed navigation requires animals to maintain a stable heading aligned with a goal, while remaining flexible enough to reorient when environmental conditions change. In the Drosophila central complex, EPG compass neurons encode heading direction, but how downstream circuitry converts these representations into adaptive steering commands remains unclear.

Downstream of EPG neurons, hΔB neurons transform heading representations into travel-direction signals and provide input to hΔA neurons. Through connections with downstream motor pathways, hΔA neurons are well positioned to convert internal navigational representations into adaptive steering commands. hΔA neurons provide input to premotor steering neurons, mainly PFL2 and PFL3, which relay navigational information to locomotor output circuits.

To test how flies adapt their steering behavior in response to changing sensory conditions, we placed head-fixed flies on a spherical treadmill within a virtual reality environment containing a salient visual landmark. During initial trials, each fly established a preferred goal direction relative to the landmark. With the goal heading identified, we introduced a transient heat stimulus coupled to the fly's heading direction.

The fly's angular deviation from its preferred goal direction determines heat intensity. A 60°

region centered ±90° from the goal heading defined a "cool zone" with minimal heat exposure. As the fly moved further outside this zone, we increased heat intensity proportionally until reaching a predefined maximum. This paradigm created a sensory incentive for flies to reorient toward the cool zone while preserving their ability to freely choose steering trajectories. We used this paradigm to compare three genotypes: flies with hΔA neurons silenced via Kir2.1 expression and two genetic controls.
Under these conditions, control flies adjusted their heading trajectories and reoriented toward the cool zone when the heat stimulus was activated. By contrast, hΔA-Kir2.1 flies exhibited straighter trajectories that were more aligned with their pre-heat heading. Furthermore, hΔA-Kir2.1 flies maintained higher forward speeds than control flies.
These findings suggest that hΔA neurons are required for flexible navigation under changing environmental conditions.

Disclosures: B.S. Moitt: None. **W. Zhang:** None. **N.L. Pettit:** None. **R.I. Wilson:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.08/LL41

Topic: I.09. Spatial Navigation

Title: Robustness through modulability: from the fly connectome to exact ring attractor dynamics

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Abstract: A cognitive compass enabling spatial navigation requires the neural representation of head direction, yet the neural circuit architecture enabling this representation remains unclear. While various network models have been proposed to explain head direction systems, these models rely on simplified circuit architectures that may be irreconcilable with empirical observations from connectomes. Here we construct a neural network model for the fruit fly head direction system that satisfies both connectome-derived architectural constraints and the functional requirement of continuous head-direction representation. To achieve this, we first characterized an ensemble of continuous attractor networks where compass neurons providing local mutual excitation are coupled to inhibitory neurons. Our multi-population model allowed us to discover a new class of ring attractor network with weaker symmetry requirements than usually assumed. For each of the four available fly connectomes, our analyses uncovered three distinct realizations of these networks. Furthermore, we found that synaptic variations among and around the fly connectomes can be compensated by cell-type-specific rescaling of synaptic weights, which could be potentially achieved through neuromodulation. The fly connectomes are

ideally configured to take advantage of this mechanism, suggesting a novel design principle linking synapse-resolution connectivity to network computation.

Disclosures: T. Biswas: None. **A. Stanoev:** None. **S. Romani:** None. **J.E. Fitzgerald:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.09/LL42

Topic: I.09. Spatial Navigation

Support: NIH Grant R01NS127129

Title: Dynamic integration of odor and valence information during olfactory navigation in Drosophila

Authors: *Y. CHEN[1], R. FARRELL[2], K. VAN HASSEL[3], K. M. NUNEZ[4], K. NAGEL[1]; [1]NYU Grossman Sch. of Med., New York, NY; [2]Columbia University,, New York, NY; [3]NYU Langone Hlth., Weatogue, CT; [4]Neurosci. Inst., New York Univ. Langone Hlth., New York, NY

Abstract: Olfactory navigation is critical for animals to locate food, shelter, and mates. In natural environments, plumes of attractive odor can be intermixed with neutral and aversive odors with varying temporal correlations. How flies integrate valence learning with time-varying concentrations of odor mixtures is not well understood. To investigate this question, we have established a two-odor delivery system that allows us to create dynamic mixtures of apple cider vinegar (ACV, an innately attractive odor) and octanol (OCT, a neutral odor) in a wind tunnel paradigm. Using this paradigm, we show that we can erase the attractiveness ACV by pairing odor presentation with optogenetic stimulation of aversive dopamine neurons. We show that this assigned valence generalizes across concentrations. We further show that we can assign either positive or negative valence to the neutral odor OCT, without impacting the innate attractiveness of ACV. When OCT and ACV are presented together, the learned aversive responses to OCT and innate attraction to ACV sum in a dynamic fashion that depends on the relative timing of these two odors. Our work illuminates both generalization and segregation of olfactory valence memories, and illustrates how valence memories are translated into dynamic behavior in the presence of conflicting cues.

Disclosures: Y. Chen: None. **R. Farrell:** None. **K. van Hassel:** None. **K.M. Nunez:** None. **K. Nagel:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.10/LL43

Topic: I.09. Spatial Navigation

Title: Hierarchical coding of categories and identities in the bat hippocampus

Authors: *E. FARBER, S. RAY, O. SPIEGEL, S. PALGI, L. LAS, N. ULANOVSKY;
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Abstract: The hippocampus plays a key role in navigation and contains place cells, neurons that encode an individual's self-location. Natural navigation occurs in complex environments that contain various categories of agents, including animals of the same or different species, and objects. However, little is known about how the hippocampus encodes these diverse categories during navigation. Here, we performed wireless neural recordings from dorsal-CA1 hippocampal neurons of wild-caught bats, as they were flying toward conspecifics (other bats), heterospecifics (humans), or objects. Hippocampal neurons encoded the category (humans/bats/objects) and identity (e.g. human1 or human2), via a mechanism of gain-modulation of place-fields ('rate-remapping'), thus preserving the spatial tuning. The hippocampal neural population enabled excellent decoding of category and identity, and formed a hierarchical code, with identity nested within the representation of category. Thus, the hippocampus forms a structured neural code of categories and identities in parallel to the classical spatial code.

Disclosures: E. Farber: None. **S. Ray:** None. **O. Spiegel:** None. **S. Palgi:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.11/LL44

Topic: I.09. Spatial Navigation

Title: Neural manifolds going wild: high-dimensional hippocampal coding in bats flying freely outdoors on a remote island

Authors: *Y. WASERMAN, S. RAY, S. PALGI, L. LAS, N. ULANOVSKY;
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Abstract: The brain evolved to support complex behavior in natural environments. However, much of what we know about neural coding comes from constrained lab experiments that, until recently, focused on single-neuron activity. Here, we combine, for the first time, large-scale neuronal population recordings with unconstrained behavior outdoors, to study the hippocampal neural manifold during natural navigation. We tracked bats with high-precision GPS and used wireless electrophysiology to record simultaneously >100 hippocampal CA1 neurons, as the

animals flew freely on an uninhabited island. Immediately before the outdoor session, we recorded the same neurons during back-and-forth flights in a small indoor room, enabling a direct comparison of neural activity across very different environments. Beyond its large spatial scale, the island offered a rich landscape - including beaches, rocks, and many landmarks - as well as more diverse behavior. Consistent with prior work in large indoor arenas, many place cells exhibited multiple place fields outdoors. Next, we estimated neuronal manifold dimensionality - both intrinsic and embedding dimensions. Indoor dimensionality was similar to previously reported results from CA1 of mice performing a virtual reality task. Strikingly, the dimensionality of the same neuronal ensembles was 2-4 times higher outdoors than indoors. Visually rich areas showed increased dimensionality. By contrast, dimensionality did not increase as a function of spatial scale, echolocation rate, or simple behavioral differences. Therefore, we attribute most of the increased dimensionality outdoors to higher cognition and/or complex aspects of behavior. Further, estimating dimensionality using random subsets of neurons showed that indoor dimensionality quickly saturated as subset size increased, whereas outdoor dimensionality continued to increase. This suggests that, by recording a larger ensemble of neurons, the measured dimensionality difference would increase further. We conclude that the low dimensionality of neuronal population activity - which has been ubiquitously reported across brain areas and species - is not a fundamental property of the brain, but rather a consequence of the behavioral and environmental simplicity of standard laboratory tasks. To reveal the full complex structure of neural activity, merely recording large neuronal populations is insufficient; instead, brain research must combine large-scale neuronal recordings with complex, unconstrained behavior.

Disclosures: Y. Waserman: None. **S. Ray:** None. **S. Palgi:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.12/LL45

Topic: I.09. Spatial Navigation

Title: Hippocampal place cells in bats navigating outdoors on a remote oceanic island

Authors: *S. RAY[1], Y. WASERMAN[1], S. PALGI[2], L. LAS[1], N. ULANOVSKY[1];
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Abstract: The mammalian hippocampus is crucial for navigation. Experiments over the last half a century have established that the dorsal CA1 region of the hippocampus is the core hub of spatial representation in the brain, and it contains place cells - neurons that encode an animal’s location. However, all these thousands of experiments have been performed in simple and constrained laboratory settings - conditions that are far removed from the natural conditions where animal brains and their behaviors have evolved. This leaves the fundamental question

unexplored - how does the brain actually represent space during unconstrained navigation in the real world? To tackle this challenge, we performed single-unit neural recordings from freely flying bats as they navigated outdoors on a remote oceanic island. To achieve this, we developed a wireless neural-logger with an integrated high-precision GPS and altimeter - allowing us to record electrophysiological activity from hundreds of single neurons simultaneously, together with the bat's position and altitude in the real world. We tracked the bats from the first day they explored this novel geographical area, and recorded their navigation behavior and dorsal hippocampal CA1 neurons as they explored the island over multiple days. We discovered hippocampal place cells outdoors - neurons that exhibited stable spatial coding in this unconstrained setting. Single place cells exhibited multi-field and multi-scale coding of space, while bats explored several thousand square meters every night. Place fields were not uniformly distributed over the island, but rather over-represented important locations. The unconstrained bats flew at different altitudes over the island, and place-fields anisotropically encoded the z-dimension. Overall, we provide here the first report on spatial coding in the mammalian hippocampus during unconstrained real-world navigation outdoors.

Disclosures: S. Ray: None. **Y. Waserman:** None. **S. Palgi:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.13/LL46

Topic: I.09. Spatial Navigation

Title: Cognitive maps for the landscape of fear in the bat hippocampus during navigation outdoors

Authors: *S. PALGI, S. RAY, O. KABLA, L. LAS, N. ULANOVSKY;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Humans and animals evolved to live in and interact with complex environments, where multiple factors govern their behavior: for example, where to forage for food, or where to avoid predators. These interactions are the focus of behavioral ecology, where a major concept is the "landscape of fear": animals are more vigilant in dangerous areas, or avoid them completely, suggesting they have a cognitive map of fear that they utilize to make spatial decisions. To date, this theory stayed within behavioral ecology, and no studies investigated the neural mechanisms underlying these fear maps. Here we recorded a unique dataset in bats navigating outdoors over an oceanic island. This natural environment had two main sources of danger for the bats: (1) the ocean, as the island was isolated and far from any other landmass and, (2) a large colony of big and predatory sea birds at the center of the island. We used the local bird density and the distance from the ocean as two metrics of danger. Bats visited less the dangerous areas in this environment, consistent with the framework of ecology of fear. While the bats explored the

island, we recorded >100 neurons simultaneously in hippocampal area CA1 - an area known for cognitive maps. We used a Poisson generalized additive model and found neurons which encoded the local bird density or the distance from the ocean, in addition to the classical place-coding expected in this brain region. We then used the neural population activity to fit a sigmoidal fear response function for each bat, whose parameters had meaningful cognitive interpretations. These neurometric functions mapped the external sources of danger (bird density, distance to ocean) into an internal representation of fear - i.e. a cognitive map of fear for each bat. These maps allowed to reliably decode the internal fear level of the bats on held-out data. Furthermore, going back to the individual neurons, we found that many of them significantly encoded the bats' internal fear level. Together, we established here that the hippocampus contains a cognitive map of fear during natural navigation outdoors. More broadly, we believe that the development of large-scale neural recordings during natural behavior in the real world will open a new field of neuroecology.

Disclosures: S. Palgi: None. **S. Ray:** None. **O. Kabla:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.14/LL47

Topic: I.09. Spatial Navigation

Title: Effects of animal movement on hippocampal CA3 spatial representations

Authors: *L. CHEN[1], S. R. MAIMON[2], L. LAS[2], N. ULANOVSKY[2], J. ALJADEFF[1];
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[2]Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Hippocampal place cells exhibit distinct spatial coding schemes when animals navigate large, dynamic environments, compared with small, simple ones. These observations constrain the neural mechanisms mediating place-cell activity during locomotion, immobility and sleep, and raise a central question: how do intrinsic circuit dynamics and movement statistics shape spatial representations, navigation, and memory consolidation? To address this question, we construct a spiking attractor model of hippocampal CA3, enabling a mechanistic account of how cellular-level heterogeneity, subthreshold dynamics and spike-frequency adaptation (SFA) govern population-level spatial coding. We find that animal movement strongly reshapes spatial representations. Within-neuron comparisons across movement speeds show that place-field locations and sizes are significantly modulated by speed, while correlations between movement-induced changes in field size and location suggest that locomotion alters the population code for position. Moreover, heterogeneity in neuronal background currents (Chen & Campbell, 2022, J Comp Neuro) affects the accuracy of neuronal spatial code. Specifically, the network is subject to a speed limit, below which it successfully tracks the animal’s position. Greater heterogeneity

improves tracking quality for faster movement, and above a critical level, enables tracking at arbitrarily high speeds.Consistent with experimental data, we propose that hippocampal networks operate in distinct heterogeneity regimes during slow and fast movement. Below a speed threshold, neurons experience nearly homogeneous background currents, and place-field sizes increase with movement speed. Above this threshold, increased heterogeneity supports reliable tracking of rapid movement and yields a much broader distribution of place-field sizes with weak speed dependence (Maimon et al., 2026, Nature). By incorporating SFA into the model, we show that competition between intrinsic adaptation and external sensory input biases forward/backward sequential place-cell activity, resembling theta sweeps observed during locomotion (Wang et al., 2020, Science). These dynamics may contribute to spatial planning and memory consolidation. Together, our model reproduces key experimental observations, including place-field variability, and its modulation by movement, heterogeneity and adaptation, and links cellular spiking mechanisms to population-level spatial representations and sequential activity, providing a biologically grounded framework for interpreting large-scale hippocampal recordings and guiding future experiments.

Disclosures: L. Chen: None. **S.R. Maimon:** None. **L. Las:** None. **N. Ulanovsky:** None. **J. Aljadeff:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.15/LL48

Topic: I.09. Spatial Navigation

Title: whole-body 3D behavioral states refine CA1 place-field estimation

Authors: *M. WEI, Y. ZHOU, J. SUN, G. SHI, F. ZAN, W. OUYANG, K. LIU;
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Abstract: Hippocampal place cells, characterized by spatially selective place fields, are essential for spatial navigation. Place-field analyses commonly use locomotor-speed thresholds to define periods of active exploration. However, it remains unclear whether this criterion is sufficiently precise to incorporate all behavioral states, such as low-speed active sampling states, or whether it conflates periods that differ in posture, orientation, limb coordination, and exploratory context. We therefore asked whether whole-body 3D behavioral structure could better identify informative epochs for CA1 place-field estimation. We developed a custom high-speed (100 - 200 Hz) multi-view 3D motion reconstruction system and a hierarchical 3D behavioral-vocabulary algorithm. The pipeline reconstructed whole-body skeletal dynamics during free exploration and transformed continuous pose trajectories into interpretable states through body-centered normalization, locomotor-state parsing, subtype discovery, manifold-density-guided refinement, and consolidation into five categories: stationary pause, vertical head-scanning

pause, horizontal head-scanning pause, walk, and run. Combining 3D behavioral recording with in vivo electrophysiology from the rat hippocampal CA1, we evaluated pose-defined inclusion rules against occupancy-matched speed-threshold controls. Transition analysis showed that horizontal head-scanning pauses were strongly coupled with the 3D behavior-defined walk state, supporting their interpretation as low-speed active exploration rather than immobility. Among all pose-defined rules, the combination of walk and horizontal head-scanning pause provided the most robust condition; adding other pause types did not yield further improvements. Relative to occupancy-matched controls, walk + horizontal head-scanning pause increased spatial information, preserved or improved place-field cleanliness, and maintained split-half stability. Cluster-aware unit-level analysis further corroborated the gain in spatial information. Together, whole-body 3D behavioral states revealed spatially informative horizontal head-scanning pauses that speed-threshold filtering has missed. The optimal rule was defined by posture- and behavior-based walking, combined with active horizontal head-scanning pauses, rather than by faster locomotion alone, highlighting the importance of whole-body behavioral context in hippocampal spatial coding.

Disclosures: M. Wei: None. **Y. Zhou:** None. **J. Sun:** None. **G. Shi:** None. **F. Zan:** None. **W. Ouyang:** None. **K. Liu:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.16/LL49

Topic: I.09. Spatial Navigation

Support: BBRF Young Investigator Grant
NIH
Simons Foundation
Gatsby Charitable Foundation
Kavli Foundation
Howard Hughes Medical Institute

Title: A new code for position - Euclidean neural maps in the mouse medial frontal cortex

Authors: *R. SEN[1], L. POSANI[3], A. MEDOFF[2], L. ABBOTT[1], R. AXEL[4], S. FUSI[2];
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[4]Zuckerman Mind Brain Behavior Inst., New York, NY

Abstract: Spatial navigation requires both direct representations of location and abstract representations of relational structure that enable extrapolation from explored to unexplored regions of space. We observed a spatial representation in the mouse medial frontal cortex (mFC) that has the geometrical properties of a flat Euclidean map in neural activity space and supports extrapolation. We performed calcium imaging of excitatory neurons in mFC (n =10 mice, 47-245

neurons/mouse), hippocampal dorsal CA1 (dCA1; n = 7 mice, 239-462 neurons/mouse), and latero-ventral orbitofrontal cortex (lvOFC; n = 6 mice, 50-137 neurons/mouse). Position could be decoded from both mFC and dCA1 populations. In mFC, linear decoders trained to predict horizontal or vertical nose position in one half of the arena generalized to the other half (extrapolation), suggesting a linear, disentangled, map-like representation of space. In contrast, dCA1 representations showed markedly reduced extrapolation, while lvOFC showed weak spatial structure overall. In mFC, but not dCA1, the Euclidean distance between locations measured in population activity space correlated with physical distance, indicating that this representation preserves spatial geometry in a form consistent with a relational map of space. Our results provide evidence for a low-dimensional, map-like representation in the mouse frontal cortex that supports extrapolation, preserves distances, and may provide a substrate for navigational planning.

Disclosures: R. Sen: None. **L. Posani:** None. **A. Medoff:** None. **L. Abbott:** None. **R. Axel:** None. **S. Fusi:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.17/LL50

Topic: I.09. Spatial Navigation

Support: ERC Synergy grant no. 95139 ("KiloNeurons")
Israel Science Foundation Grant 1922/24
Gatsby Charitable Foundation

Title: Origins of hippocampal spatial selectivity via E-I balance

Authors: *N. MAINALI[1], S. R. MAIMON[3], L. LAS[4], N. ULANOVSKY[4], Y. BURAK[2];
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[3]Neurobio., [4]Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Our understanding of the hippocampal spatial code remains largely phenomenological and primarily centered on excitatory place cells, leaving the underlying circuit mechanisms unresolved. A critical barrier is the poorly understood role of inhibitory interneurons, which are classically viewed as uniform background regulators. To uncover the role of interneurons in shaping the CA1 spatial code, we recorded simultaneously from CA1 pyramidal cells and interneurons in bats navigating a large, ethologically relevant 200-m tunnel. Contrary to the classical view, we found that interneurons exhibit dense, highly fluctuating, and reliable spatial maps. These tuning curves closely matched the statistics of stationary Gaussian processes—a dense, unthresholded counterpart to the sparse spatial code of pyramidal cells, which we previously showed is captured by a thresholded Gaussian process. In addition, we observed substantial heterogeneity across the interneuron population in their underlying spatial statistics,

with the properties of individual neurons stably preserved across flight directions. We next asked whether a mathematical theory could explain how the CA1 circuit simultaneously generates these diverse Gaussian-process-based spatial codes and the substantial cell-to-cell heterogeneity. We derived an anatomically constrained recurrent network model operating in an excitation-inhibition (E-I) balanced state. Constrained only by coarse population means, this theoretical framework quantitatively reproduces both the dense interneuron Gaussian process statistics and the sparse pyramidal place fields. It organically produces the broad, structured heterogeneity of single-neuron tuning properties, along with the heavy-tailed firing rates and highly dispersed, Gamma-Poisson field counts in pyramidal cells. Furthermore, the balanced network explains coding "propensity"—the stable preservation of a neuron's statistical identity across remapped contexts—as a permanent imprint of its recurrent synaptic connectivity. Collectively, these results bridge the algorithmic and implementational levels of hippocampal spatial coding, elevating inhibition from a modulatory role to an active, representational substrate of the cognitive map.

Disclosures: N. Mainali: None. **S.R. Maimon:** None. **L. Las:** None. **N. Ulanovsky:** None. **Y. Burak:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.18/LL51

Topic: I.09. Spatial Navigation

Title: Fast intrinsic dynamics decouple stability and flexibility in neural sequence generation

Authors: *I. VOITOV[1], A. MUSAD[2], C. SANTHIRASEGARAN[1,3], A. SHAH[1], A. LOSONCZY[3];
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Abstract: Neural systems must transform stochastic or ambiguous sensory signals into context-appropriate internal representations to enable efficient memory allocation and retrieval. The hippocampus exhibits sequential population activity patterns across multiple timescales that reorganize across contexts, and such dynamics have been proposed to support both attractor-mediated stabilization of sensory inputs into learned representations (“mapping”) and transitions between stable attractor states when inputs change (“remapping”). Recurrent circuitry in hippocampal area CA3 has been implicated in generating these dynamics, but it remains unclear how a fixed network architecture can selectively amplify context-specific trajectories within a shared neural state space. To investigate this, we used two-photon optogenetic stimulation to drive CA3 neurons in precisely timed sequences with varied temporal order and lag, enabling measurement of the intrinsic interactions shaping population dynamics. We uncovered dense interactions whose strength and sign varied smoothly with stimulation lag at tens-of-milliseconds

resolution. Closed-loop stimulation of place field sequences observed during spatial navigation further revealed network recruitment that was specific to nearby place fields, consistent with an autoassociative attractor architecture. We integrated the measured lag-dependent interactions and autoassociative connectivity to construct a “Synaptic Kernel RNN” for dynamical analysis of mapping and remapping. Simulations showed that these networks preserved sensitivity to changing inputs even when activity exhibited strong pattern completion under high recurrent gain, unlike classical attractor networks that impose a trade-off between stabilization and input steering. This flexibility arose from an uncoupling of recurrent support from motion along the attractor manifold: transient instabilities when recent input history aligned with the lag-dependent recurrent kernel enabled input steering, while global stability was maintained as this alignment rapidly decayed. Consistent with this, Synaptic Kernel RNNs exhibited broader controllability and sustained marginally separable trajectories over longer timescales relative to standard dimensionality-matched RNNs. Together, these results demonstrate that fast intrinsic dynamics in CA3 generate reservoirs of flexible spatiotemporal sequences, thus linking millisecond-scale circuit interactions to behavioral-timescale computation in the brain.

Disclosures: I. Voitov: None. **A. Musad:** None. **C. Santhirasegaran:** None. **A. Shah:** None. **A. Losonczy:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.19/LL52

Topic: I.09. Spatial Navigation

Support: ERC Synergy 101167367

Title: Neural bases of temporal cognitive maps of auditory sequences

Authors: *J. JOUVION[1], B. BATHELLIER[2];
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Abstract: Being able to represent and organize experienced events over time is a key element to infer causations and predict future events. However, the existence, structure, and neuronal implementation of temporal cognitive maps remain elusive. Previous studies have indicated that various brain regions including posterior parietal cortex may be involved in second-to-minute timing. Through large scale electrophysiology, we were able to record thousands of neurons in 4 different brain areas (auditory cortex, AC, parietal cortex, PPC, hippocampus, HPC, and temporal associative cortex, TEa) to investigate the emergence and characteristics of temporal cognitive maps. We demonstrated that mice can passively learn to predict reward timing in a sound sequence and generalize this timing information when sounds are masked. We showed that in the PPC, HPC and TEa of trained mice, the population activity progressed linearly along a neural manifold that stretched over the whole sequence, and that this manifold was robust to

sound removal. By contrast, auditory cortex rather encoded sound identity. This neural manifold was absent in naïve, non-rewarded mice. Finally, we found that while these three regions encode information about time in the sequence, the neuronal activity underlying this temporal manifold differ greatly across regions: while PPC activity is organized in a sparse sequential firing chain across time, units in TEa seem to redundantly ramp up to reward time, and HPC units have hybrid response profiles with a strong phasing to sounds.

Disclosures: J. Jouvion: None. **B. Bathellier:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.20/LL53

Topic: I.09. Spatial Navigation

Support: R01NS101108
I01RX003498
1I01BX006511-01

Title: Electrophysiological Characterization of the Porcine Hippocampus During Freely Moving Behavior and Cognitive Tasks

Authors: *E. MIRZAKHALILI[1,2], A. V. ULYANOVA[2,3], H.-C. I. CHEN[2,3], J. A. WOLF[2,3]; [2]Neurosurg., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]CMC VA Med. Ctr., Philadelphia, PA

Abstract: The hippocampus is integral to learning and memory, and its dysfunction underlies cognitive deficits across neurological disorders. Much of our knowledge regarding the electrophysiological characteristics of the hippocampus derives from years of rodent studies. While valuable, rodents are limited translational models because neither their brain structure (non-gyrencephalic) nor their nocturnal behavior closely resembles that of humans. Conversely, non-human primates are excellent translational models, but their use is constrained by ethical and practical concerns. Swine models have the potential to bridge this gap between rodent and non-human primate neurophysiological studies. Here, we utilized wireless technology to perform long-term, chronic hippocampal recordings in freely moving male Yucatan miniature swine (n=11) within their home cages and during cognitive tasks such as an alternating T-maze. We localized the pyramidal layer by maximum ripple power (80-250 Hz) and the stratum radiatum by peak sharp-wave amplitude, then averaged co-occurring sharp-wave ripples (SWRs) for current-source density (CSD) analysis to build a standardized laminar profile across animals to compare local field potentials (LFPs). During locomotion, we observed robust theta oscillations that were notably slower (5-6 Hz) than typical rodent rhythms (7-8 Hz). Locomotor states also exhibited prominent theta-gamma phase-amplitude coupling. In contrast, periods of immobility and non-REM sleep were characterized by SWRs, though porcine ripple frequencies (~100 Hz) were slower than those seen in rodents (~180 Hz). Leveraging extracellular spike features, we

classified single units into putative pyramidal cells and interneurons, demonstrating that these populations are dynamically entrained to ongoing theta and gamma oscillations and tightly phase-locked to SWRs. Finally, a subset of these units exhibited spatial modulation consistent with place cell activity during T-maze navigation. Moreover, during awake rest periods between alternation trials, these spatially tuned ensembles exhibited sequential reactivation consistent with forward and reverse replay of the behavioral track. Collectively, these findings validate the utility of the freely moving swine model, demonstrating that while core circuit motifs, cell-type entrainment, and candidate replay-based consolidation mechanisms appear conserved, porcine network oscillations operate at lower frequencies. This model provides a robust, translationally relevant platform for investigating hippocampal circuit dynamics in cognitive health and disease.

Disclosures: E. Mirzakhalili: None. **A.V. Ulyanova:** None. **H.I. Chen:** None. **J.A. Wolf:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.21/LL54

Topic: I.09. Spatial Navigation

Support: National Medical Research Council (MOH-000962)

Title: Place and view responses are multiplexed in the primate Hippocampus during virtual navigation

Authors: R. HERIKSTAD[1], H. TAN[2], P. NG[1], C. B. OWENS[4], C. LIBEDINSKY[3], ***S.-C. YEN**[1];
[2]The N.1 Inst. for Hlth., [3]Psychology, [1]Natl. Univ. of Singapore, Singapore, Singapore; [4]Inst. for Mol. and Cell. Biol., Agency for Science, Technol. and Res., Singapore, Singapore

Abstract: The responses of cells in the primate hippocampus during navigation have received increased focus in recent years. Unlike the responses of the neurons in the rodent hippocampus, which mainly appears to encode allocentric spatial coordinates, primate hippocampus cells exhibit a mix of both spatial and view related responses. This mix has been linked to the greater importance of vision during navigation in these species. Indeed, evidence now suggests that this reliance on vision creates a “viewpoint” coding of space, where specific visual scenes are stitched together using path integration mechanisms to form an egocentric navigation code. In this study, we recorded the activity of hippocampal cells as a non-human primate subject was navigating a virtual reality maze. We used a mesh representation of the floor and walls of the maze to get a high-resolution representation of the place and view fields of each of the recorded cells. We computed the Spatial Information Criterion (SIC) on maps obtained by smoothing firing rates binned according to the subjects location in the maze, and the location of their gaze on maze, to classify cells as selective to space and view. A total of 364 cells were recorded, of

which 198 (54.4%) were found to be place selective and 122 (33.5%) view selective. Among the spatially selective cells, 134 (67.7%) had at least one clearly defined place field. Among the view selective, 80 (65.5%) had at least one clearly defined view field. In addition, 104 (28.6%) were both place and view selective. We further divided these so-called putative mixed selective cells into subgroups. First, we excluded cells that had oriented place fields. This is because if these cells exhibited preferences over certain traversal directions through their place fields, they could be identified as view selective, even though they really only encoded spatial features. We found that 15 (31.3%) of the place and view selective cells had oriented place fields. For the remaining place and view selective cells, we looked for cells where the place and view responses were not independently represented. Using a conditioning procedure that carefully corrected for dependencies induced by the maze topology and the behavior of the subject, we found 35 (72.9%) of the cells showed significant dependencies between their place and view responses. These results add to the growing body of evidence suggesting that primate hippocampal cells encode complex relationships between spatial location within environments and the visual inputs associated with those environments, and emphasize the increased role that vision serves in primate compared to rodent navigation.

Disclosures: R. Herikstad: None. **H. Tan:** None. **P. Ng:** None. **C.B. Owens:** None. **C. Libedinsky:** None. **S. Yen:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.22/LL55

Topic: I.09. Spatial Navigation

Support: 2019R1A2C2088799
2022M3E5E8017723
RS-2024-00452391
RS-2025-02303740

Title: Run or drive: The role of voluntary attention in hippocampal place coding

Authors: *S. PARK[1], E.-H. LEE[1], S.-M. LEE[2], I. LEE[1];
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Abstract: Active navigation facilitates spatial map formation, whereas passive navigation often limits it, suggesting that cognitive map formation requires voluntary attention (VA) for allocentric cues. We hypothesized that VA enables the hippocampus to integrate task-relevant sensory and action-related information into coherent maps. We recorded CA1 single-unit activity in body-fixed rats (n=6) performing a VR spatial memory task requiring scene-guided stops in the reward zone. During active navigation, rats ran on a treadmill or drove by pressing a lever on

a linear track in pseudo-random order (50 trials/block); stops were concentrated near the reward zone in both modalities (>70%). Place cells (spatial information >0.1, $p<0.01$) were more frequently observed in Running (57%) than Driving (22%). Population maps covered the track in both modalities, indicating that spatial firing was not restricted to the reward zone. Most place cells were active in only one modality, and among cells active in both modalities, 78% showed global remapping, suggesting VA supports context-specific map formation. We tested passive navigation to determine whether spatial coding is disrupted when movement no longer controls task-relevant sensory progression. We used an ABA design with Active1 (A1), Passive (P), and Active2 (A2) blocks. In A1- and A2-blocks, rats performed active navigation using the same modality, either Running or Driving. In P-blocks, rats could run or press the lever, but VR position advanced at random speed independent of their movement. Thus, passive navigation removed the movement-to-scene coupling present during active navigation. CA1 place cell proportions were lower in P-blocks than in A1- and A2-blocks, with many P-block cells exceeding the spatial information threshold but few passing the shuffle criterion (Driving: A1 30%, P 4%, A2 28%; Running: A1 65%, P 8%, A2 65%). During P-blocks, rats in both modalities continued moving until the VR scene reached the reward location and reduced movement afterward, suggesting that their movements remained task-oriented. Because these movements no longer controlled VR position, continued reward-location-directed movement may reflect VA toward task-relevant cues rather than motor control of navigation. Future analysis will use movement during passive navigation to classify sessions into high- and low-VA groups and test whether higher task-related movement is associated with higher CA1 place cell proportions.

Disclosures: S. Park: None. **E. Lee:** None. **S. Lee:** None. **I. Lee:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.23/LL56

Topic: I.09. Spatial Navigation

Support: NRF 2019R1A2C2088799
NRF 2019R1A2C2088799
NRF 2022M3E5E8017723
NRF RS-2024-00452391
NRF RS-2025-02303740
the Mid-Career Bridging Program through Seoul National University

Title: Functional coexistence and dissociation of robust place and spatial view codes in the primate hippocampus

Authors: *S. SHIN[1], H.-Y. LIM[2], S.-M. LEE[1], J.-M. SEOL[3], C.-H. LEE[4], Y. NAYA[5], J. LEE[6], I. LEE[3];

[1]Dept. of Brain & Cognitive Sci., [3]Brain and Cognitive Sci., [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [4]Ctr. for Neurosci. Imaging Res., Inst. for Basic Sci., Suwon, Korea, Republic of; [5]Peking Univ., Beijing, China; [6]Dept. of Biomed. Engin., Sungkyunkwan Univ., Suwon-Si, Gyeonggi-Do, Korea, Republic of

Abstract: The hippocampus is central to spatial navigation and memory, yet its spatial code appears to differ across species. In rodents, place cells — neurons that fire whenever the animal occupies a particular location — are the dominant spatial correlate, characterized during active navigation along linear tracks. In non-human primates (NHPs), by contrast, hippocampal studies have more commonly reported spatial view cells, which fire according to where the animal looks rather than where it is. Because these findings rest on markedly different paradigms, we asked whether position-selective cells emerge in the primate hippocampus when NHPs navigate a linear track — the canonical rodent place-cell paradigm. To address this, we recorded single-unit activity from the hippocampus of two macaques performing an object-in-context memory task in virtual reality (VR). On each lap, the animal entered either a forest or a city environment and navigated a linear track by joystick in both outbound and inbound directions, giving four task conditions (forest/city × outbound/inbound). At predefined locations, the animal was stopped to choose the object rewarded in the current context. Both macaques reached >96% accuracy. To identify the variables encoded by individual neurons, we applied a generalized linear model (GLM) encoding analysis, classifying each unit as position-coding, view-coding, or conjunctive according to whether position, the visual scene (view), or both significantly contributed to its firing. Of the 113 neurons recorded, 87.7% coded spatial information — position and/or view — in at least one condition. All three classes were present in every condition: view-coding was most prevalent (~21-26%), but position-coding cells were also robustly represented (~11-20%), alongside conjunctive cells (~6-12%), and each class's proportion was stable across conditions. Position cells further showed place-cell hallmarks—localized, stable fields that remapped with both direction and context. Population decoding confirmed that these classes are functionally grounded: neurons assigned to position or to view decoded their respective variable better than control populations, indicating that the GLM classes capture genuine, decodable information. Together, these findings establish position as a genuine coding dimension of the primate hippocampus — present, decodable, and not merely incidental to the scene in view — when NHPs navigate under conditions matched to the rodent paradigm, suggesting its rarity in earlier NHP studies reflects, at least in part, differences in experimental setting rather than a fundamental species difference.

Disclosures: S. Shin: None. **H. Lim:** None. **S. Lee:** None. **J. Seol:** None. **C. Lee:** None. **Y. Naya:** None. **J. Lee:** None. **I. Lee:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.24/LL57

Topic: I.09. Spatial Navigation

Support: NRF 2019R1A2C2088799
NRF 2022M3E5E8017723
NRF RS-2024-00452391
NRF RS-2025-02303740
Mid-Career Bridging Program through Seoul National University

Title: Stepwise recruitment of CA3 spatial maps via nonlinear state transitions governed by visual ensembles and scene complexity

Authors: *E.-H. LEE, I. LEE;
Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Despite the powerful influence of visual stimuli on hippocampal place cells, the conditions needed to recruit a spatial map from a quiescent baseline remain unclear. Our previous work revealed that CA1 responds to individual landmarks, whereas CA3 requires a visual ensemble (Shin et al., 2022). To extend these findings, we aimed to delineate the environmental conditions and circuit-level mechanisms underlying de novo CA3 recruitment. We simultaneously recorded single-unit and local field potential (LFP) activity in CA1 and CA3 of body-restrained Long-Evans rats (n=8) navigating virtual linear tracks. As discrete landmarks were parametrically scaled from 2 to 20 against a black background, CA1 place cells continuously updated their spatial tuning by incorporating additional landmarks into an established spatial framework. Conversely, CA3 demonstrated a nonlinear recruitment profile. Its place cell proportions remained at a quiescent baseline (~10%) until multiple landmarks formed a spatiotemporally integrated visual ensemble, triggering an abrupt increase (~20%). Moreover, evaluating environments of varying scene complexity revealed that highly complex naturalistic scenes with continuous backgrounds acted as a spatial scaffold, eliciting a further increase (~60%). These results establish visual ensembles and scene complexity as distinct conditions driving stepwise CA3 recruitment. Crucially, these single-unit dynamics tightly paralleled network state transitions in theta-gamma phase-amplitude coupling (PAC). During the initial ensemble-driven recruitment, CA3 exhibited a selective reduction in fast gamma PAC, reflecting the attenuation of external sensory inputs from the entorhinal cortex. Following further activation in complex scenes, the network displayed a significant increase in slow gamma PAC, indicating enhanced internal recurrent processing. Collectively, these findings demonstrate that CA1 functions as a continuous integrator of environmental features, whereas CA3 operates as a scene constructor via nonlinear state transitions. By first isolating the nascent map from external noise and subsequently engaging intense internal synchronization, the hippocampus ensures a balance between representational stability and flexibility.

Disclosures: E. Lee: None. **I. Lee:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.25/LL58

Topic: I.09. Spatial Navigation

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0205000)

Title: Encoding Traveled Distacne by Visual and Inertia Motion Signals in Parietal Cortex

Authors: *C. ZHANG[1], Y. GU[2];
[1]Ctr. for Excellence in Brain Sci. and Intelligence Technol., Shanghai, China; [2]Syst. neuroscience, Inst. of Neurosci., Shanghai, China

Abstract: Precisely estimate self-travelled distance is crucial for individuals to interact with environments. Instantaneous self-motion signals, including visual motion (e.g., optic flow) and inertial motion (vestibular), broadly exist in the brain, yet how they are integrated over time and across modality for coding a long time scale of distance concept is elusive. Here we trained macaques to estimate their translated distance (long vs. short) based on either inertial motion or optic flow cues. After training, the nonhuman primates could reliably use either cue to discriminate long vs. short travelled distance, rather than the elapsed time. Importantly, the performance was significantly improved during bimodal stimulation when both cues were available, in a way consistent with Bayesian optimal integration predictions. Neural recordings in the parietal cortex, including IPS and MSTd/STS regions, revealed two major forms of distance coding: transient distance tuning and sustained ramping activity. Several findings suggest that transient distance coding may play a more direct role in self-motion distance computation, including: i) transient neurons were the dominant type of distance-coding neurons across recorded regions; ii) transient distance-coding neurons in IPS were functionally coupled with the animals' perceptual choice on a trial by trial basis; and iii) during bimodal stimulation, transient neurons in IPS tended to exhibit enhancement, which might mediate optimal integration in the behavior. These results suggest that transient distance coding, especially in IPS, may support cross-modal distance integration and behavioral distance judgments.In summary, our findings identified and favored a transient code for computation of travelled distance by the primates' parietal neurons, which may be further read out by downstream areas (e.g. HPC, PFC).

Disclosures: C. Zhang: None. **Y. Gu:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.26/LL59

Topic: I.09. Spatial Navigation

Support: The Marian C. Diamond & Arnold B. Scheibel Fund in Neuroscience
NIH Grant 4RF1MH131624-03

Title: Spatial planning during virtual navigation in non-human primates

Authors: *H. LIANG[1], J. D. WALLIS[2];
[1]UC Berkeley, Berkeley, CA; [2]U.C. Berkeley, Berkeley, CA

Abstract: Planning often enables one to achieve goals more efficiently, yet its underlying neural computation remains poorly understood. To investigate planning at single-neuron resolution, we developed a virtual navigation task for non-human primates in which animals used a joystick to navigate a 2D virtual maze towards a rewarded target. At any given moment, only the local environment but not the full maze layout was visible to animals. Therefore, to efficiently navigate towards the target, animals are required to mentally construct and use an internal model of the maze structure. To encourage flexible route planning, the target location changed across blocks and the start location was randomized within each block. Animals successfully reached the target on 49.2% of trials, outperforming simulated agents without an explicit knowledge of the maze. An agent with a random policy succeeded on only 18.1% of trials and a Q-learning agent on 20.7%, under identical task conditions. Furthermore, animals exhibited significantly longer reaction times on failed trials than on successful ones ($p<10\text{-}6$), indicating that more deliberation is needed when the path towards the target is not readily apparent. Together, these results suggest that animals acquired knowledge of the maze structure and likely planned a trajectory prior to navigation. Simultaneous recordings from the hippocampus and orbitofrontal cortex will be performed to examine how their coordination supports the sequential representation of states and rewards during planning.

Disclosures: H. Liang: None. **J.D. Wallis:** None.

Poster

PSTR248: Place, Direction, and Navigation II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR248.27/LL60

Topic: I.09. Spatial Navigation

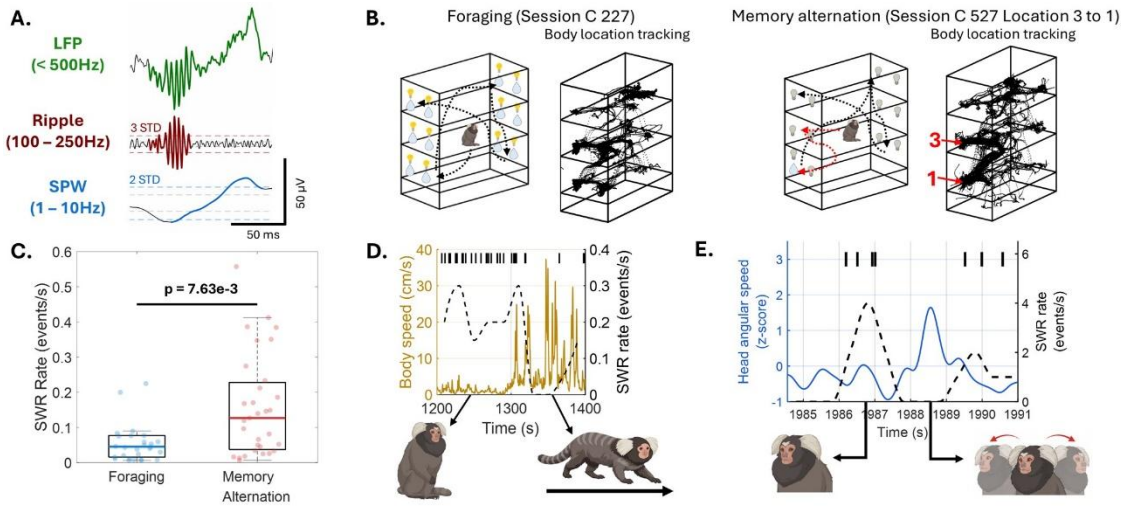
Support: NIEH T32ESO33955
Canadian Institute of Health Research Project Grant (CIHR)
Natural Sciences and Engineering Research Council of Canada (NSERC)
Provincial Endowed Academic Chair in Autism
Canada Foundation for Innovation (CFI)
Western University BrainsCAN award grant and Healthy Brains
Wallace Coulter Foundation

Title: A Conserved Hippocampal Navigation Motif Reconfigured for Primate Vision

Authors: *C. OTERO[1], D. B. PIZA[3], E. ABOUTORABI[5], J. C. MARTINEZ-TRUJILLO[4], J. J. RIERA[2];
[2]Biomed. Engin., [1]Florida Intl. Univ., Miami, FL; [4]Dept. of Physiol. and Pharmacol. and

Psychiatry, [3]Western Univ., London, ON, Canada; [5]Robarts Res. Institute, Western Univ., London, ON, Canada

Abstract: Hippocampal sharp wave-ripples (SWRs) are brief local field potential events implicated in memory retrieval, consolidation, and planning. Although SWRs are well characterized in freely moving rodents, their relationship to spatial navigation in freely moving primates remains largely unknown. Here, we wirelessly recorded hippocampal local field potentials from three common marmosets navigating a 3D maze during foraging and memory-guided alternation tasks, while simultaneously tracking body position and head orientation. We developed an observer-validated SWR detector combining coincident sharp-wave (1-10 Hz) and ripple-band (100-250 Hz) criteria, detecting 19,481 manually curated SWRs across 49 sessions. Marmosets navigated by alternating between locomotion and pauses, spending most recorded time paused while performing rapid head movements that visually sampled the maze. SWR rates were higher during pauses than locomotion in both foraging (median: 0.059 vs. 0.018 events/s, p = 0.003) and memory alternation (0.29 vs. 0.02 events/s, p = 0.0001), and this difference persisted after duration-matched temporal equalization. Memory alternation further increased SWR rates relative to foraging (median = 0.12 vs. 0.04 events/s; p = 7.63e-3), shortened inter-event intervals (median = 2.20 vs. 2.42 s; p = 2.35e-32), and markedly lengthened ripple duration (median = 155 vs. 100 ms; p = 4.8e-282). During pauses, SWR rates were highest when head direction was stationary and aligned with reward-associated subregions, and reward-related modulation was stronger for head direction than body position alone. Together, these findings identify a conserved navigation motif in which hippocampal SWRs preferentially occur during pauses, while revealing a primate-specific visual specialization in which reward-directed head orientation shapes SWR dynamics during memory-guided navigation.



Analyzing SWRs in a freely moving Marmoset during a foraging and memory alternation task. A. Example of a SWR. Top is the LFP signal, Middle is the ripple band (100–250 Hz) with detected ripple component in red, bottom is the SPW bandpass (1-10 Hz) with detected SPW component in blue. Scale bar on bottom right for all panels. **B.** Two cartoon illustrations, on the left is for the foraging task and the right is the memory alternation task (red indicating the reward alternation that needed to be followed for reward). To the right of each is the body traces for one session recording of each task (alternation locations numbered in red as well). **C.** Session-level SWR rates were significantly higher during memory alternation than foraging (Wilcoxon rank-sum test, one-tailed; n=29 foraging sessions, n=30 memory alternation sessions; $p = 7.63 \times 10^{-3}$). **D.** Body-speed trace from one session segment showing locomotion and pause periods with SWR events marked by vertical ticks. **E.** Example of head angular-speed trace during a body pause in a single session segment showing SWR events marked by vertical ticks. In **D** & **E** are black arrows pointing toward illustration to represent movement of animal.

Disclosures: C. Otero: None. **D.B. Piza:** None. **E. Aboutorabi:** None. **J.C. Martinez-Trujillo:** None. **J.J. Riera:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.01/LL61

Topic: J.03. Anatomical Methods

Support: STI 2030-Major Projects Grant 2022ZD0211902
STI 2030-Major Projects Grant 2021ZD0202205
NSFC Grant 32293210
NSFC Grant 32171461

Title: Connectomic Organization of the Suprachiasmatic Nucleus

Authors: *J. LIU[1], J. YU[2];
[1]Inst. of Automation Chinese Acad. of Sci., Beijing, China; [2]PKU-Nanjing Inst. of Translational Med., Nanjing, China

Abstract: The suprachiasmatic nucleus (SCN), the mammalian master clock, is a special structure dedicated to the time computation. However, a connectomic understanding of the nucleus as a whole is lacking. Using serial section electron microscopy, we reconstructed multiscale and multimodal SCN communication networks. Intra-SCN synaptic network consists of 9,762 morphologically similar neurons and 4.3 million synapses, organized into multiscale circuitries that interact with SCN-traversing axon fascicles. Strikingly, SCN neurons engage in unique soma-soma ephaptic interaction, forming 2,579 electrotonic integrative units with the largest overlapping the light-responsive area (LRA). SCN's paracrine modality contains 47,396 μm^3 dense core vesicles, with notable scarcity in the LRA, suggesting cross-modal coordination and functional integration. These distinct network features provide comprehensive insights into the system architecture of the mammalian circadian clock.

Disclosures: J. Liu: None. **J. Yu:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.02/LL62

Topic: J.03. Anatomical Methods

Title: muDM: A Multi-Format Spatial Data Model forML-Native Bioimaging

Authors: *B. LJUNGQUIST, N. SCHAUB;
NovaGen Res. Fund, North Bethesda, MD

Abstract: Modern neuroscience produces high resolution spatial annotations at a scale that strains conventional tooling. Dense connectomes, whole-brain neuron reconstructions, and spatially resolved molecular maps each contain millions of features. Connecting the different components (visualizations, extracted and experimental features, etc) has been a challenge both for data linking and utility. Annotations must serve different consumers: machine-learning training, interactive 3D visualization, and 2D map-style browsing. No single format supports all three well, so groups maintain parallel pipelines and re-encode the same data repeatedly. We present muDM (micro Data Model), a spatial data model and tiling pipeline that addresses this fragmentation. The data model extends the widely used GeoJSON vocabulary to microscopy coordinates, 3D geometry, and biological metadata, giving 2D and 3D annotations one uniform representation. Its companion pipeline, mudm-tools, builds a single spatial index over a dataset and emits several standard output formats from it: a columnar format suited to machine-learning training, a 3D tile format for web viewers, and standard vector tiles for 2D mapping. Feature and tile identity are preserved across every format, and level-of-detail simplification lets large meshes and annotation sets stream at an appropriate resolution. Because the outputs are established standards rather than bespoke encodings, they connect directly to existing 3D and 2D viewers, common mapping libraries, and machine-learning data loaders. We demonstrate muDM across connectomics, neuron morphology, spatial transcriptomics, and digital pathology, including training a 3D point-cloud classifier directly on tiled connectome data. By letting curation, model training, and visualization operate on the same spatial features without re-conversion, muDM is a reusable substrate for cross-modality analysis of large neuroscience imaging datasets.

Disclosures: B. Ljungquist: None. **N. Schaub:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.03/LL63

Topic: J.03. Anatomical Methods

Support: Brain Science and Brain-like Intelligence Technology - National Science and Technology Major Project (2021ZD0204401 to S.J.X.; 2021ZD0204503 to K.W.)
National Natural Science Foundation of China (32125020 to K.W.; 32371072 to S.J.X.; 32321003 to K.W. and S.J.X.; 32300936 to L.C.)
Shanghai Committee of Science and Technology, China (22JC1403101 to K.W. and S.J.X.)
Strategic Priority Research Program of the Chinese Academy of Sciences (XDB1010102 to K.W.)
China Postdoctoral Science Foundation (2023M743609 and BX20240389 to L.B.)

Title: Trimodal integration of in vivo functional imaging, whole-brain morphology, and gene expression in single neurons

Authors: ***L. BAI**[1], Y. ZHAO[3], Z. SHI[3], X. LIU[4], L. CONG[3], Y. ZHANG[1], L. GU[3], C. JIN[3], T. ZHANG[5], N. XU[6], S. XU[7], K. WANG[2];
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Abstract: Understanding how neuronal function emerges from the interplay of molecular identity, morphological architecture, and circuit connectivity remains a central challenge in neuroscience. While recent advances have enabled separate high-throughput characterization of in vivo activity, whole-brain projections, and gene expression, integrating all three modalities within the same neuron has remained unrealized — primarily due to challenges in preserving structural and molecular integrity across sequential experimental stages. To address this gap, we developed an Imaging-based Multimodal Characterization (IMC) platform that sequentially acquires functional, structural, and molecular data from individual neurons. For functional imaging, we performed in vivo two-photon Ca^{2+} imaging in awake, head-fixed mice with sparsely labeled neurons in the primary visual cortex (VISp). Neurons were presented with checkerboard and drifting grating stimuli, and their responses were characterized using a generalized linear model (GLM) framework. Facial movement signals were simultaneously recorded to account for behavioral state modulation. In total, Ca^{2+} activity was recorded from 207 neurons across 12 mice, revealing distinct functional populations: checkerboard-dominant, grating-dominant, co-responsive, movement-correlated, and non-responsive neurons. Following functional imaging, the same neurons were subjected to whole-brain morphological reconstruction and in situ transcriptomic profiling via 2cEASI-FISH, yielding complete trimodal profiles for 141 cortical projection neurons. Trimodal integration revealed that checkerboard-dominant neurons exhibited markedly reduced axonal arborization, distinct subcellular RNA localization patterns, and elevated Rbp4 expression compared to other functional groups. Furthermore, combining Vip expression with somatic location identified a specialized pyramidal tract (PT) subtype co-activated by both checkerboard and nasal-ward drifting grating stimuli. Functional validation using Rbp4-Cre mice confirmed that Rbp4 serves as a reliable molecular marker for checkerboard-responsive neurons. Together, the IMC platform establishes a robust framework for linking in vivo neuronal function to molecular and structural identity at single-neuron resolution, opening new avenues for dissecting the molecule-structure-function relationships underlying cortical computation.

Disclosures: L. Bai: None. **Y. Zhao:** None. **Z. Shi:** None. **X. Liu:** None. **L. cong:** None. **Y. Zhang:** None. **L. Gu:** None. **C. Jin:** None. **T. Zhang:** None. **N. Xu:** None. **S. Xu:** None. **K. Wang:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.04/LL64

Topic: J.03. Anatomical Methods

Title: Non-destructive tissue ultrastructure and elemental mapping at the new CORUS beamline of the ALBA synchrotron

Authors: *C. BOSCH PIÑOL[1,2], J. IHLI[1], E. SOLANO[1], A. PATERA[1], J. NICOLAS[1], J. JUANHUIX[1];
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Abstract: Maps of biological tissues at subcellular to ultrastructural detail hold key insights to mechanistically understand how organs and organisms work. In the brain, these maps provide the location, morphology and connectivity of all cells inside - the connectome. Volume electron microscopy is the current golden standard for connectomics[1], yet hard X-ray nanoimaging brings important advantages:
- X-rays can penetrate >mm into heavy metal-stained tissues with preserved ultrastructure, enabling non-destructive 3D imaging without slicing the sample
- X-ray phase contrast imaging resolved 4nm detail in computer chip samples[2] and 40nm detail in brain tissue[3]
- 4th generation synchrotrons create X-ray beams with enough flux to image petavoxels in days[4]
The new CORUS beamline at the upgraded 4th generation ALBA2 synchrotron (Spain) will host two endstations devoted to multiscale and multimodal imaging of biological cells and tissues. NanoImag will welcome tissue samples of 50 µm - 1 mm in diameter for nanoimaging with X-ray holographic nanotomography at room temperature, and nanoFluoSpec will accommodate hydrated cell samples in cryogenic conditions, for 3D elemental mapping and speciation using X-ray fluorescence microscopy and spectroscopy. CORUS will support a petascale data processing pipeline and will enable correlative multimodal imaging workflows. These coherent imaging efforts will be paralleled locally with a materials sciences-focused beamline, CoDI. These two new beamlines join the existing imaging workforce at ALBA led at the cm^3 scale & µm detail by FAXTOR (hard X-ray propagation-based phase retrieval), at the 400-2000 µm^3 scale & 50 nm detail by MISTRAL (soft X-ray tomography in the water window), and at the macromolecular scale by a cryo electron tomography facility. Altogether, the ALBA2 synchrotron places itself at the forefront of biological research, enabling multimodal workflows to interrogate the structure and function of biological systems across scales - from molecules to tissues and organs.

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4 Du, M. *et al.* Upscaling X-ray nanoimaging to macroscopic specimens. *J Appl Crystallogr* **54**, 386-401, doi:10.1107/S1600576721000194 (2021).

Disclosures: C. Bosch Piñol: None. **J. Ihli:** None. **E. Solano:** None. **A. Patera:** None. **J. Nicolas:** None. **J. Juanhuix:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.05/LL65

Topic: J.03. Anatomical Methods

Support: Eric and Wendy Schmidt
The Riley and Susan Bechtel Foundation
James Fickel
Hearst Foundations

Title: Self-correcting neuron tracing for dense light microscopy connectomics

Authors: H. G. J. DAMSTRA, J. LYUDCHIK, J. M. MICHALSKA, A. SHERIDAN, A. APOLONIO, R. N. ARRUDA, A. S. CHAMPION, S. W. CHAN, J. CHEN, M. ISBRECHT, J. LEE, C. A. MAGNO, R. MENG, E. MURRAY, W. PATTON, J. L. RHOADES, M. WU, J. Y. AXUP, K. G. C. LEEPER, J. WINNUBST, *A. C. PAYNE;
E11 Bio, Alameda, CA

Abstract: Light microscopy methods have the potential to revolutionize connectomics by radically improving accessibility and reducing cost. Recently, we introduced PRISM (Protein-barcode Reconstruction by Iterative Staining with Molecular annotations), a scalable platform for accurate neuron tracing that integrates combinatorial AAV delivery of cell-filling protein barcodes, highly multiplexed expansion microscopy readout, and automated barcode-guided segmentation. Here, we extend that platform to include dense morphological readout using >16-fold expansion microscopy. We show the combination of protein barcodes with dense morphology can be leveraged to bridge spatial gaps, e.g. between non-continuous tissue sections, to improve accuracy of machine learning-based segmentation, and to facilitate automated proofreading. These advances are integrated into an end-to-end light microscopy connectomics pipeline centered on PRISM, from viral labelling to automated detection and assignment of excitatory synapses in automatically proofread neurons. Going forward, we anticipate that PRISM will overcome key challenges relating to scale and cost in light microscopy connectomics.

Disclosures: H.G.J. Damstra: None. **J. Lyudchik:** None. **J.M. Michalska:** None. **A. Sheridan:** None. **A. Apolonio:** None. **R.N. Arruda:** None. **A.S. Champion:** None. **S.W. Chan:** None. **J. Chen:** None. **M. Isbrecht:** None. **J. Lee:** None. **C.A. Magno:** None. **R. Meng:** None. **E. Murray:** None. **W. Patton:** None. **J.L. Rhoades:** None. **M. Wu:** None. **J.Y. Axup:** None. **K.G.C. Leeper:** None. **J. Winnubst:** None. **A.C. Payne:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.06/LL66

Topic: J.03. Anatomical Methods

Title: Low-dimensional organization of long-range axonal projections in the mesoscopic connectome

Authors: *T. SONG, C. LIU;
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Abstract: A major advance in mesoscopic connectomics has been the brain-wide reconstruction of long-range axons, revealing extensive diversity in neuronal projection patterns. Yet, even when individual axonal trees are densely reconstructed, their global structural logic remains difficult to interpret because each neuron is represented as a high-dimensional and highly branched morphology. To address this problem, we developed a computational framework that decomposes complex axonal projections into combinations of topologically constrained projection modules. In this framework, each axonal tree is represented by a compact set of recurring components, enabling substantial compression of morphological feature space while maintaining anatomical interpretability. We applied this approach to more than 40,000 neurons aggregated from public datasets. The resulting model identified a compact dictionary of basic projection patterns, with the top 10 patterns accounting for 80.1% of total reconstructed axonal length. Several inferred patterns corresponded closely to known fiber tracts, supporting the biological plausibility of the decomposition, whereas others lacked clear correspondence to canonical tract annotations and may represent previously under-characterized mesoscale projection motifs. We further applied the algorithm to non-human primate datasets and identified projection patterns shared across mouse, marmoset, and macaque, suggesting part of the mesoscopic connectome is organized by evolutionarily conserved structural motifs. Together, these results suggest that the observed diversity of long-range axonal morphologies can be described using a low-dimensional set of recurring structural patterns. This representation provides a scalable strategy for comparing projection architecture across neurons, brain regions, datasets, and species, and may help uncover how the mammalian brain's wiring diagram is structurally and evolutionarily organized.

Disclosures: T. Song: None. **C. Liu:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.07/LL67

Topic: J.03. Anatomical Methods

Support: STI 2030-Major Projects 2022ZD0205200

Title: An integrative platform for cross-species mesoscale mapping of nervous system

Authors: *Y. E. XIAO[1], Y. SHEN[1], C.-Y. YANG[2], F. XU[3], H. WANG[4], S. LI[5], Q. XIAO[1], P. LAU[6], G. BI[1,5];
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Abstract: Large-scale mesoscale microscopy datasets are increasingly available across species, but their value is often limited by fragmented workflows for reconstruction, storage, publication, visualization, and annotation. These problems are especially acute for primate and human brain samples, for which remote sharing is essential. Here we present CereVi, an integrative platform for cross-species mesoscale mapping of the nervous system built around the Volumetric Imaging with Synchronized on-the-fly-scan and Readout (VISoR) pipeline. CereVi connects specimen processing, volumetric reconstruction, multiscale packaging, remote visualization, remote annotation, and region-aware analysis within one framework.
CereVi adopts OME-Zarr as the native container for reconstructed and derived image data, with VISoR-specific metadata and organization that preserve acquisition context while remaining interoperable with external tools. The platform supports datasets from mouse brain, whole-body mouse, macaque brain, rhesus macaque neuronal tracing, and human brain. Through a web interface, users can inspect coronal, sagittal, and horizontal views, navigate multiscale image pyramids, examine local three-dimensional blocks, and access atlas-linked region information without downloading full datasets. Orthogonal slices, region overlays, and tiled annotation workflows support collaborative use on very large images.
To illustrate the analytical value of this shared image pipeline, we outline a region-aware cross-species workflow linking volumetric image blocks, cell segmentation, anatomical annotation, and quantitative comparison of cell-shape features across matched brain regions. The same infrastructure can also support tracing-oriented and tract-oriented downstream analyses. CereVi provides a practical framework for turning PB-scale datasets into remotely accessible, annotation-ready, and analysis-capable resources for comparative mesoscale mapping from mouse to human.

Disclosures: Y.E. Xiao: None. **Y. Shen:** None. **C. Yang:** None. **F. Xu:** None. **H. Wang:** None. **S. Li:** None. **Q. Xiao:** None. **P. Lau:** None. **G. Bi:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.08/LL68

Topic: J.03. Anatomical Methods

Title: A Scalable Hierarchical Framework for Petabyte-Scale Volumetric Image Stitching and Registration

Authors: ***C.-Y. YANG**[1], G.-Q. BI[2];
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Abstract: Large-scale 3D microscopy produces petabyte-scale volumetric data with complex non-rigid deformations, yet existing tools lack the scalability for seamless stitching and registration. We propose a scalable hierarchical framework that decomposes massive workflows into manageable local registration tasks via AI-assisted task planning. The framework is built upon deep learning-based registration with specialized strategies for challenging scenarios—including narrow-overlap, non-overlapping, and cross-modal cases—to achieve high-precision stitching for diverse mesoscale imaging modalities such as light-sheet microscopy and electron microscopy. It adopts a hierarchical multi-scale blockwise paradigm enabling scalable computation, delivering high performance and flexible processing of petabyte-scale data, and providing essential infrastructure for brain atlas and connectome construction.

Disclosures: C. Yang: None. **G. Bi:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.09/LL69

Topic: J.03. Anatomical Methods

Support: STI 2030 Major Program (Grant No. 2021ZD0200104; 2022ZD0205200)

Title: Whole-brain single-neuron mapping reveals fine-scale organization of primate thalamocortical pathways

Authors: ***Y. SHEN**[1], L. DING[2], S. LI[3], X. HU[4], Y. XIAO[1], F. XU[1], G.-Q. BI[1,3];
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Abstract: Classical thalamocortical pathways have been defined mainly by population-level tracing and physiological studies, yet their whole-brain organization at single-neuron resolution in primates remains poorly understood. Building on a previously established VISoR-based platform, we mapped primate thalamic single neurons by integrating sparse viral labeling, micron-resolution whole-brain imaging, fiber tracing, and cytoarchitecture-guided brain parcellation and projection annotation. Using this workflow, we reconstructed more than 1,000

thalamic neurons across the lateral geniculate nucleus (LGN), mediodorsal nucleus (MD), ventral posterolateral nucleus, and lateral dorsal nucleus, generating a large-scale whole-brain single-neuron dataset for the primate thalamus.
Analysis of representative sensory and higher-order thalamic nuclei revealed distinct projection strategies. In the LGN, single-neuron projections followed the classical visual thalamocortical framework while revealing finer organization, including projection subtypes across V1 sublayers, discrete eye-related terminal clusters that may shape structured and orientation-biased feedforward inputs, and rare axonal bifurcations to multiple visual cortical areas that suggest a potential role in cross-areal integration. In contrast, MD neurons exhibited broad multi-target projections across Brodmann areas and cortical functional modules. Projection-based clustering identified distinct MD subtypes with different target combinations, and local cortical patches appeared to receive input from MD neurons sharing local targets but diverging in distal collaterals.
Together, these findings advance primate thalamocortical connectivity from a population-level framework to a fine-scale single-neuron model in which distinct projection subtypes, axonal branching patterns, and local terminal architecture support both precise local processing and distributed cortical network coordination.

Disclosures: Y. Shen: None. **L. Ding:** None. **S. Li:** None. **X. Hu:** None. **Y. Xiao:** None. **F. Xu:** None. **G. Bi:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.10/LL70

Topic: J.03. Anatomical Methods

Support: NIH Grant R01NS125307

Title: Connectional neuroanatomy of U-fibers in the rhesus monkey brain

Authors: *T. J. CAPEN[1,2], G. BLANCHARD[2], M. H. YAHAYA[2], L. J. O'DONNELL[3], E. H. YETERIAN[5], Y. RATHI[4,6], N. MAKRIS[2,4,6], D. L. ROSENE[2], R. J. RUSHMORE, III[2,4,6]; [2]Anat. & Neurobio., [1]Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA; [3]Radiology, [4]Psychiatry Neuroimaging Lab., Brigham and Women's Hosp., Boston, MA; [5]Psychology, Colby Col., Waterville, ME; [6]Psychiatry, Ctr. for Morphometric Analysis, Massachusetts Gen. Hosp., Boston, MA

Abstract: The superficial white matter (SWM) is the component of the cerebral white matter located immediately beneath the gray matter-white matter (GM-WM) border. It primarily contains short corticocortical association fibers thought to play an important role in local cortical information processing. Within the SWM, U-fibers are classically depicted using dissection as U-shaped bundles coursing superficially beneath sulci to interconnect adjacent gyri. This led to

the conception of the SWM as a ubiquitous layer of symmetric short association pathways that interconnects adjacent gyral regions. However, the prevalence, trajectory, and connectional organization of U-fibers have not been systematically evaluated using experimental tract tracing and remain poorly defined. To address this gap, we analyzed 28 archival tract-tracing cases in the rhesus macaque with anterograde tracer injections placed in gyri adjacent to four major sulci (principal, central, intraparietal, and superior temporal), each with clear correspondence to human sulci. The GM-WM border was delineated in counterstained sections, allowing the trajectories, termination patterns, and depth of tracer within the white matter to be assessed. Although short association fibers were identified in all cases, U-fibers, defined as fibers passing beneath a sulcus and terminating on the adjacent gyrus, were observed beneath the major sulci in only 36% of cases, with incidence varying by sulcus. U-fibers were always present under the principal and central sulci but were infrequently observed beneath the intraparietal and superior temporal sulci. When present, the U-fibers could be short and orthogonal to the sulcal axis or longer and highly oblique to connect more distant areas along the sulcus. Association bundles shorter than U-fibers were frequently identified under all sulci. These bundles terminated along the proximal sulcal bank (L-type) or crossed the fundus to the opposing bank without reaching the adjacent gyrus (J-type). Analysis of fiber bundle depth also revealed a consistent 200-300 μm band directly beneath the GM-WM border that contained short association fibers approaching their terminations but was avoided by deeper long association pathways. Unlike U-fibers, which were sulcus-specific, this superficial band was present in all sulci examined. U-fibers were observed both within and below this band. Histological data using diverse markers confirmed the presence of this band. Together, these findings show that U-fiber organization is more complex than previously understood and likely relates to specific patterns of cortical connectivity rather than sulcal geometry.

Disclosures: T.J. Capen: None. **G. Blanchard:** None. **M.H. Yahaya:** None. **L.J. O'Donnell:** None. **E.H. Yeterian:** None. **Y. Rathi:** None. **N. Makris:** None. **D.L. Rosene:** None. **R.J. Rushmore:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.11/LL71

Topic: J.03. Anatomical Methods

Support: NIH Grant R24MH114785
NIH Grant RO1MH126684

Title: BossDB 2.0: The Archive for Petascale Neuroimaging and Connectomics

Authors: *D. XENES, J. MATELSKY, C. A. BISHOP, T. GION, N. GUITTARI, R. T. HIDER, Jr., E. C. JOHNSON, H. MARTINEZ, P. K. RIVLIN, N. E. TREGONING, B. A.

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Abstract: The NIH BRAIN Initiative Informatics Program was created to establish data archives, consensus standards, and tools for neuroscience. As part of this effort and the broader BRAIN data ecosystem, the Brain Observatory Storage Service and Database (BossDB) serves as an NIH-supported data archive for storage of, access to, and analysis of high-resolution electron microscopy (EM), X-ray micro- and nanotomography, and related connectomics and neuroimaging datasets. BossDB currently stores more than five petavoxels of data and, consistent with FAIR principles, provides scalable access to expanding datasets across species, modalities, and research communities. Here, we present BossDB 2.0, a major platform release that uses cloud-native infrastructure to streamline services and improve support for data discovery, access, annotation, processing, and analysis. The BossDB 2.0 architecture is built around a serverless data plane that abstracts storage complexity while supporting direct cloud reads, format-aware routing, and on-demand conversion across precomputed, Zarr, and related formats. Frequently accessed data can be served directly from object storage through edge routing, while compute-backed requests are routed to scalable services and cached as reusable derived outputs. The BossDB 2.0 API, Python SDK, and documentation expose these capabilities transparently to users and developers. BossDB 2.0 also unifies metadata, provenance, permissions, and data paths through a schema-first information layer, enabling versioned metadata updates, audit trails, owner-managed access controls, taxonomy and modality validation, and explicit links among source data, derived products, annotations, and analysis outputs. In parallel, a generalized asynchronous job platform supports ingest, downsampling, indexing, rechunking, meshing, skeletonization, and enrichment workflows with trackable status, throttling, and reproducible execution. These infrastructure changes strengthen BossDB integrations with community frameworks and tools, including Neuroglancer, NeuVue, NeuPrint, DotMotif, CAVE, NeuroGlass, and AI-assisted search and annotation systems. Together, BossDB 2.0 advances the platform from an archival data repository toward a shared scientific workspace that reduces the technical burden of petascale connectomics and helps researchers move more directly from data access to biological discovery.

Disclosures: D. Xenes: None. **J. Matelsky:** None. **C.A. Bishop:** None. **T. Gion:** None. **N. Guittari:** None. **R.T. Hider:** None. **E.C. Johnson:** None. **H. Martinez:** None. **P.K. Rivlin:** None. **N.E. Tregoning:** None. **B.A. Wester:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.12/LL72

Topic: J.03. Anatomical Methods

Title: Lychnis Viewer: a scalable software tool for large-volume connectomic visualization and neuron reconstruction

Authors: *L. DING[1], Y. SHEN[2], F. XU[3], Y. XIAO[4], G.-Q. BI[5];
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Abstract: Connectomic studies increasingly use micrometer-resolution volumetric imaging to reconstruct long-range neuronal projections across whole brains and other large biological specimens. These datasets can reach tens to hundreds of terabytes, making it difficult to load, navigate, and reconstruct neuronal morphology while preserving anatomical context. We developed Lychnis Viewer, a software tool for large-volume connectomic visualization and neuron reconstruction. The tool combines CUDA-accelerated out-of-core volume rendering with real-time coordinate transformation for data access. Rather than relying on fully precomputed multiresolution copies, Lychnis Viewer generates a virtual multilevel data pyramid during navigation. This allows users to move between whole-specimen views and micrometer-scale neurites with reduced storage redundancy, and supports interactive inspection of large datasets such as macaque whole-brain and mouse whole-body volumes.
Lychnis Viewer also includes a video-production workflow for large volumetric datasets. Making videos from TB-scale microscopy data often requires downsampling, cropping, or high-end computing resources because each adjustment to color, channels, or timing may require repeated 3D rendering. To reduce this overhead, Lychnis Viewer separates computationally expensive volume rendering from later visual editing. Users can pre-render 16-bit intermediate sequences and then adjust color mapping, channel composition, camera timing, annotations, and export settings through lightweight script-based composition. This workflow makes it easier to produce videos from large biological volumes while retaining access to the rendered structural information.
To improve interoperability, Lychnis Viewer provides an HTTP-based communication protocol for external programs or AI agents. Through a set of mapped Skills, external commands can trigger native actions such as dataset loading, camera navigation, atlas-region lookup, neuron-tracing assistance, quantitative measurement, and batch export. This design allows Lychnis Viewer to be incorporated into semi-automated analysis workflows without changing the underlying reconstruction interface. Together, these functions provide a practical tool for large-volume connectomic analysis, supporting visualization, video generation, and reconstruction of long-range neuronal projections in whole-brain and whole-body microscopy datasets.

Disclosures: L. Ding: None. **Y. Shen:** None. **F. Xu:** None. **Y. Xiao:** None. **G. Bi:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.13/LL73

Topic: J.03. Anatomical Methods

Support: NIH UM1NS132253

Title: Automated Cutting and Collection of Mouse Brain Hemisphere sections for Synapse-resolution Connectome imaging

Authors: ***X. LU**[1], S. J. COOK[1], J. SCHARDT[1], A. GUTHRIE[2], S. VASQUEZ[1], C. DEVINE[1], K. M. GRUVER[1], M. M. TAKENO[1], D. BRITTAIN[1], M. WOODARD[1], R. REID[1], N. M. DA COSTA[1];
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Abstract: A structural connectome with synapse resolution provides a comprehensive wiring diagram of the brain, unveiling the cell type constitution, circuit building principles, and eventually will provide insights into disease diagnostics and inspire new artificial intelligence models. To date, the largest connectome of a mammalian brain are cubic-millimeter volumes acquired from mouse visual cortex (MICrONS project) or human (H01 volume). While the MICrONS project already provided unprecedented multimodal understanding of the brain and motivated new scientific questions, it still represents only about 1/1000 of whole mouse connectome. To move beyond local circuit fragments and reveal how distributed cell types and long-range pathways are organized across the brain, a more complete connectome that spans the whole mouse brain is of great desire.One critical challenge to scaling up the connectome with synapse resolution is the physical sectioning of the brain—ensuring consistent, and with minimal loss serial cutting of ultrathin sections across centimeter-scale volumes, which estimates to be 150,000 – 250,000 sections for a single hemisphere, or 2-3 months of consecutive cutting and collecting onto an electron-transparent film. Work at this scale suggests the whole pipeline needs to be fully automated, requesting minimum human intervention and being able to fail or resume gracefully at unforeseen circumstances. In this work, we focused on scaling up the cutting and collection of the whole mouse hemisphere sample preparation, a critical leap towards a whole mouse brain connectome. We introduce here a customized ultramicrotome, Omnitome, that can section sample size at the whole mouse brain scale – a scale that is not achievable with commercialize ultramicrotomes. After the sample get sections, we introduced Loop-based Automated Serial Sectioning Operation (LASSO) collection method, in which a loop is used to transfer the sections from the cutting boat to electron-transparent substrates. Both Omnitome and LASSO are assisted by machine vision, making smart decisions on their ‘observations’, and pause gracefully and notify human users when unexpected events occur.To accommodate LASSO for hemisphere collection, we designed a new wafer-like substrate that can hold hemisphere sections on electron-transparent film, that will be imaged with Transmission Electron microscopy (TEM), a cost-effective, parallelizable, and non-destructive method to map synaptic connectivity. However, the technologies presented here are also suitable for other nanoscale imaging technologies that depend on cutting and collecting sections at the whole mouse brain scale.

Disclosures: X. Lu: None. **S.J. Cook:** None. **J. Schardt:** None. **A. Guthrie:** None. **S. Vasquez:** None. **C. Devine:** None. **K.M. Gruver:** None. **M.M. Takeno:** None. **D. Brittain:** None. **M. Woodard:** None. **R. Reid:** None. **N.M. da Costa:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.14/LL74

Topic: J.03. Anatomical Methods

Support: Allen Institute Proteomics Initiative
NIH Grant U01NS142100-01

Title: Multiscale imaging of molecular cell types for connectomics in mouse visual cortex

Authors: *K. L. VILLALOBOS[1], K. TAKASAKI[5], E. E. TURSCHAK[7], A. ALI[2], E. GUADARRAMA[1], W.-Q. YU[1], L. ELABBADY[3], C. LAUGHLAND[4], R. TORRES[1], E. PERLMAN[1], N. M. DA COSTA[7], R. REID[6];
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Abstract: The organization of cortical circuits depends on the spatial relationships among molecular cell identity, cellular morphology, and synaptic connectivity. Advances in electron microscopy (EM) connectomics have revealed highly specific wiring patterns and previously unrecognized cell types in mouse primary visual cortex (VisP) based on the latter, namely morphology and connectivity. However, the molecular identities of many structurally defined types remain unknown. To bridge molecular and structural information within the same tissue context, we apply light microscopy-based connectomics (LICONN; Tavakoli et al., 2025) with fluorescent immunostaining of cell-type-associated markers within mouse VisP. Using multiscale lightsheet imaging, we acquire large-volume datasets containing antibody-derived molecular signals together with near-EM-resolution anatomical ultrastructure for dense reconstruction of cellular morphology and connectivity. Preliminary results indicate that a subset of antibody targets, such as those of inhibitory interneurons (PV, VIP, SST, etc.), remain detectable following LICONN processing and expansion, supporting the feasibility of incorporating molecular labeling into expanded connectomic tissue. Future work will incorporate multiplexed molecular labeling into this framework, allowing multiple cell-type-associated markers to be mapped onto the same connectomic tissue volumes for molecular annotation of structurally defined cell types and their spatial organization within visual cortical circuits. We will present these technical advances as well as preliminary results of analysis of corresponding molecular with anatomical cell types in these multimodal data.

Disclosures: K.L. Villalobos: None. **K. Takasaki:** None. **E.E. Turschak:** None. **A. Ali:** None. **E. Guadarrama:** None. **W. Yu:** None. **L. Elabbady:** None. **C. Laughland:** None. **R. Torres:** None. **E. Perlman:** None. **N.M. da Costa:** None. **R. Reid:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.15/LL75

Topic: J.03. Anatomical Methods

Support: U01NS136405
R01EY030138
RPB-Stein Award
GRF-CFC3

Title: Multiplexed Anterograde Transsynaptic Tracers Enable Brain-Wide Mapping of Postsynaptic Connectivity

Authors: *S. CHANG[1], J. HU[1], S. KHEM[2], R. KUTSAL[2], F. WANG[1], Y. ZHENG[1], L. LU[1], E. H. FEINBERG[1], S. YAO[2], X. DUAN[1];
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Abstract: Understanding how neuronal circuits are organized requires approaches that can directly identify neurons that are connected across the brain. Existing mapping methods primarily characterize axonal projections, thereby limiting direct fluorescence visualization and quantitative analysis of postsynaptic neurons at both whole-brain scale and cell-type resolution. We developed a fusion of the red fluorescent protein mCherry with codon-optimized wheat germ agglutinin (mWGA-mCherry), which maintains its ability for trans-neuronal transfer (PMID: 35524141). However, this method is limited by single-channel imaging. We aimed to broaden the spectral range of functional WGA fusions by incorporating green, red, and blue fluorescent proteins, enabling multiplexed tracing and validation. We systematically evaluated multiplexed anterograde tracing in vivo in both bottom-up (from retina to superior colliculus) and top-down (from primary visual cortex (V1) to thalamus) pathways. We validated the efficacy and specificity of the newly engineered fluorescent anterograde tracers using orthogonal ChR2-assisted circuit-mapping approaches. To circumvent antibody staining protocols and increase signal-to-noise ratios, we implemented serial two-photon tomography to directly visualize the anterograde trans-neuronal tracer in post-synaptic cells across the brain. This labeling was quantitatively measured at the mesoscopic scale. Using the retina as a starting point, we revealed robust postsynaptic labeling across major retinorecipient targets, including the superior colliculus, dorsal lateral geniculate nucleus, olivary pretectal nucleus, suprachiasmatic nucleus, and other retinorecipient nuclei. The direct imaging-based framework enabled brain-wide visualization and CCF registration of postsynaptic neurons, generating a brain-wide connectivity map from the retina to the brain. Using similar approaches, our ongoing efforts expanded to other brain circuits. The expanded toolkit enabled multiplexed tracing of parallel circuits within the same brain and supported conditional connectivity mapping from genetically defined starter populations. These findings establish a robust, scalable framework for multiplexed, brain-wide mapping of postsynaptic connectivity. This platform enables simultaneous visualization and quantification of postsynaptic connections across diverse neural circuits.

Disclosures: S. Chang: None. **J. Hu:** None. **S. Khem:** None. **R. Kutsal:** None. **F. Wang:** None. **Y. Zheng:** None. **L. Lu:** None. **E.H. Feinberg:** None. **S. Yao:** None. **X. Duan:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.16/LL76

Topic: J.03. Anatomical Methods

Support: NIH 5UM1NS132253-02
NIH 5U24NS120053-03

Title: Connectome Annotation Versioning Engine: Modernizing community proofreading, annotation, and analysis of connectomics datasets

Authors: D. BRITTAIN[1], ***F. C. COLLMAN**[1], S. DORKENWALD[2], A. HALAGERI[3], C. JORDAN[1], B. D. PEDIGO[1], C. M. SCHNEIDER-MIZELL[1], K. WILEY[1];
[1]Allen Inst., Seattle, WA; [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]Zetta AI, Princeton, NJ

Abstract: Advances in microscopy, segmentation, and computing have facilitated large-scale connectomics datasets, increasingly shared as community resources. These datasets are continuously edited, proofread, and analyzed by many users, creating data representation and management challenges for the computational infrastructures that host them. The Connectome Annotation and Versioning Engine (CAVE) solves these challenges and has been used to host many connectomics datasets across the field, including community resources, such as the MICrONS, FlyWire, H01, FANC, and BANC datasets. Here, we present an update to CAVE with recent additions and improvements to scale CAVE to larger datasets and enable more sophisticated analyses. We improved the generation and accessibility of cell representations, such as skeletons. Users can request skeletons directly from CAVE servers, which precompute them for specific cells to achieve fast query times. We further enabled Neuroglancer to display these skeletons directly alongside the segmentation and added support for annotations such as synapses. These annotations remain up to date with proofreading and allow users to visualize a neuron's connectivity right after editing its morphology. Because annotation tables can be challenging to access at scale, we added support for bulk access to large tables. This balances the needs of users interested in analyzing all annotations within a brain (e.g., of hundreds of millions of synapses) with the limitations of services deployed in the cloud. CAVE now enables exporting annotation tables to common static table formats, which allow for fast dataset-scale queries. Finally, we improved the ChunkedGraph implementation to reduce deployment costs, which would have been prohibitive for scaling beyond current datasets. As CAVE scales to larger datasets and more communities, we believe these new features will help users visualize, analyze, and manage their connectomics data more effectively.

Disclosures: D. Brittain: None. **F.C. Collman:** None. **S. Dorkenwald:** None. **A. Halageri:** A. Employment/Salary (full or part-time):; Zetta AI. **C. Jordan:** None. **B.D. Pedigo:** None. **C.M. Schneider-Mizell:** None. **K. Wiley:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.17/LL77

Topic: J.03. Anatomical Methods

Title: Functional Networks Underlying Perceived Limb Ownership in Alien Limb Phenomenon

Authors: *E. M. DURHAM, A. MARKER, R. FITT, M. KLEINMAN, K. GILL, N. WADE, J. A. NIELSEN;
Brigham Young University, Dept. of Psychology, Provo, UT

Abstract: Alien Limb Phenomenon (ALP) is a neurological disorder characterized by impaired motor agency and involuntary limb movements that appear purposeful or semi-purposeful, often conflicting with conscious intent. While many individuals with ALP experience a perception of loss of limb ownership, this is not universal. Prior studies have examined the functional networks associated with ALP, but differences in networks between patients who retain limb ownership and those who do not remain poorly understood. We conducted a literature review of published ALP case reports identified through PubMed and Embase. Studies were screened using predefined inclusion criteria and selected through CADIMA. Reports were included if they contained lesion-based neuroimaging, were published in English, and demonstrated a temporal relationship between the lesion and ALP symptoms. Lesions were manually traced onto a standardized brain template using 3D Slicer. Lesion network mapping was performed using a normative resting-state functional connectivity dataset to generate functional connectivity maps for each lesion. Lesion-derived networks were then overlaid in a sensitivity analysis to identify regions of significant functional overlap while controlling for the effects of general brain lesions. Positive sensitivity analyses revealed that lesions in patients who retained limb ownership and lesions in patients who experienced a loss of ownership were both functionally connected to the precuneus and body of the corpus callosum. However, lesion networks associated with retained limb ownership were uniquely connected to the splenium of the corpus callosum and cuneus, whereas lesion networks associated with loss of ownership were uniquely connected with the insula. These findings suggest that distinct functional brain networks may underlie differences in perceived limb ownership among patients with ALP. This study advances understanding of the neural mechanisms underlying ALP and provides a foundation for future investigations of limb ownership and motor control.

Disclosures: E.M. Durham: None. **A. Marker:** None. **R. Fitt:** None. **M. Kleinman:** None. **K. Gill:** None. **N. Wade:** None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.18/LL78

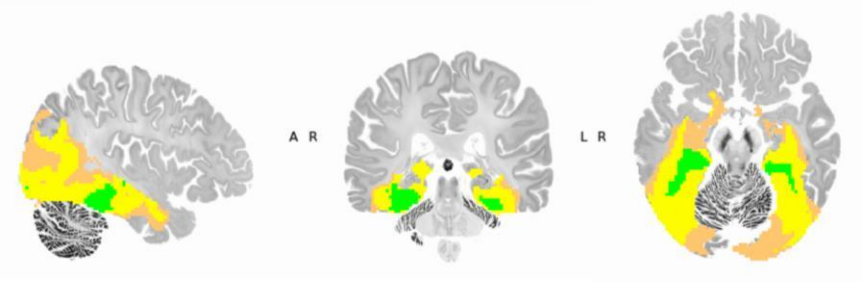
Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Distributed Face-Recognition Networks in Acquired Prosopagnosia

Authors: *C. DAVID[1], A. MARIN[2], B. ROBINSON[2], J. A. NIELSEN[3];
[1]Dept. of Psychology, [3]Psychology, [2]Brigham Young Univ., Provo, UT

Abstract: Acquired prosopagnosia is a disorder of facial recognition associated with lesions in distributed occipitotemporal and anterior temporal regions. Prior Lesion Network Mapping (LNM) studies suggest that these anatomically distinct lesions may localize to common functional networks underlying face processing. This study aimed to replicate and extend prior LNM findings in acquired prosopagnosia.Lesions from published acquired prosopagnosia case reports were traced onto a standardized brain atlas and analyzed using LNM with resting-state functional connectivity data from a normative cohort (BrainGenomics Superstruct Project, N = 1000). Sensitivity, specificity, and conjunction analyses were performed to identify networks selectively associated with prosopagnosia. Sensitivity analysis demonstrated convergent connectivity across 42 of 44 lesion-derived networks, primarily involving theright lateral occipital cortex and adjacent early face-processing regions. Specificity analysis against10,000 control lesions with unrelated symptoms identified connectivity concentrated in the right anterior temporal lobe, a region associated with identity processing. Conjunction analysis revealed overlap within the right fusiform gyrus and occipitotemporal cortex, extending into inferior temporal regions associated with broader face-processing systems. These findings are consistent with prior lesion network mapping studies and further support the hypothesis that acquired prosopagnosia reflects dysfunction within distributed face-processing networks spanning both perceptual and identity-related systems. Finalized lesion tracings and metadata were prepared for contribution to LesionBank.org to support future replication and open scientific use.



Conjunction analysis demonstrating overlap between sensitivity and specificity maps in right fusiform and occipitotemporal regions.

Disclosures: C. David: None. **A. Marin:** None. **B. Robinson:** None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.19/LL79

Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Lesion Network Mapping Identifies a Distributed Visual Network Associated with Palinopsia

Authors: *Z. HANSEN[1], N. KILLIAN[2], J. A. NIELSEN[3];
[1]Dept. of Psychology, [3]Psychology, [2]Brigham Young Univ., Provo, UT

Abstract: Palinopsia is an acquired visual disturbance characterized by persistent or recurring images after stimulus removal. It is most common following focal brain injuries. Affected individuals may report images lingering after a stimulus is removed, moving objects leaving perceived trails, or previously viewed scenes reappearing spontaneously. It is frequently underrecognized clinically and lacks established treatment, in part because its neural system remains poorly understood. Despite reports linking palinopsia to heterogeneous posterior cortical lesions, no unifying neural mechanism has been established. Traditional lesion mapping pinpoints where damage occurs but fails to capture how that damage disrupts broader brain networks. Lesion Network Mapping (LNM) addresses this by using resting-state fMRI data from healthy subjects to identify which networks are functionally connected to lesion sites, revealing shared circuit-level dysfunction across patients with the same symptom. LNM potentially clarifies palinopsia's pathophysiology and reveals targets for intervention. We conducted a systematic literature search (PubMed/Embase, PRISMA) identifying 27 human cases of lesion-induced palinopsia with available neuroimaging. Lesions were manually traced onto an MNI152 template (3D Slicer) by two raters. Functional connectivity was computed per lesion using a normative connectome from 1,000 healthy subjects (Brain Genomics Superstruct Project). Sensitivity, specificity, and conjunction analyses isolated network regions selectively associated with palinopsia versus a large, heterogeneous control lesion dataset spanning diverse neurological symptoms (Petzsche et al.), processed through an identical pipeline to ensure comparable specificity. Despite anatomical heterogeneity, network overlap revealed convergent functional connectivity. The inferior fronto-occipital fasciculus was connected to 26/27 lesions (96%) and the occipitotemporal gyrus to 24/27 (89%). Conjunction analysis identified a core node present in 25/27 cases (93%), mapping a distributed network across occipital, occipitotemporal, and fronto-occipital regions. Palinopsia appears to arise from disruption of a distributed visual network rather than focal damage, suggesting that long-range visual pathways have a central role in its pathogenesis, and supporting network-level neuromodulation as a potential treatment strategy.

Disclosures: Z. Hansen: None. **N. Killian:** None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.20/LL80

Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Lesion network mapping to differentiate neural circuits that underlie disorders of diminished motivation.

Authors: *A. R. MARKER, E. DURHAM, H. HINDMAN, R. BRYSON, J. LILYQUIST, B. MAUGHAN, K. GILL, N. WADE, J. A. NIELSEN;
Dept. of Psychology, Brigham Young Univ., Provo, UT

Abstract: Disorders of Diminished Motivation (DDMs) are characterized by a decrease of self-initiated speech, and movement. Our study utilizes Lesion Network Mapping (LNM) to compare the lesion derived neural networks causing DDMs, including akinetic mutism, athymhormia, abulia, and apathy. Utilizing PubMed and Embase we gathered clinical neuroimaging reports of patients with a temporal association between the lesion onset and DDM. These clinical cases were separated into two groups: those who spoke or moved in response to stimuli, and those who did not. To investigate brain regions functionally connected to lesion sites, LNM analysis was performed to compare and contrast overlapping networks with a large cohort of healthy control resting-state scans (n = 1000). The network sensitivity analyses of DDMs were then isolated in contrast to the networks of other neurological symptoms thereby specifying the lesion-derived neural networks of DDMs. We used LNM to both analyze the networks of all DDM cases and the comparison between the two levels of DDM intensity. When analyzing the neural circuitry of all lesions causing DDMs, 75% were functionally connected to the anterior cingulate cortex, body of the corpus callosum, and precuneus. Analysis of patients who responded to a stimuli or command had underlying neural circuitry damage in relation to the anterior cingulate cortex or the body of the corpus callosum. 75% of akinetic mutism cases with no initiation after stimuli or command had lesions functionally connected to the precuneus. This study clarifies the circuit heterogeneity of DDMs, thereby differentiating treatment locations for individuals with varying degrees of DDMs. Further research is necessary to connect these neural circuits to mechanistic therapies for DDM patients.

Disclosures: A.R. Marker: None. **E. Durham:** None. **H. Hindman:** None. **R. Bryson:** None. **J. Lilyquist:** None. **B. Maughan:** None. **K. Gill:** None. **N. Wade:** None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.21/LL81

Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Lesion Network Mapping of Hallucinations: A Structural and Functional Connectivity Analysis

Authors: *A. O. YILDIRIM[1], J. A. NIELSEN[2];
[1]Dept. of Psychology, Brigham Young Univ., PROVO, UT; [2]Dept. of Psychology, Brigham Young Univ., Provo, UT

Abstract: Lesions causing hallucinations have been reported in many different brain regions, suggesting that hallucinations may arise from disruption of shared brain networks rather than damage to a single location. Kim et al. (2021) supported this hypothesis by demonstrating a common functional network across lesion-induced hallucination cases. In the present study, we replicated these findings and extended this work by examining structural disconnectome patterns associated with lesion-induced hallucinations. Seventy-eight lesions from published cases of hallucinations were traced onto the standard MNI152 brain template and analyzed using functional lesion network mapping and structural disconnectome methods. Functional conjunction maps and structural overlap maps were generated to identify regions commonly associated with hallucinations across cases. The functional analysis replicated the main findings reported by Kim et al., showing common involvement of cerebellar and superior temporal regions despite diverse lesion locations. Structural disconnectome analysis also revealed overlap across cases involving cerebellar, brainstem, and broader white matter pathways. However, structural overlap appeared more distributed than the functional network findings, with a maximum overlap of approximately 48% of cases and no single structural region shared by half or more of the lesions. These findings suggest stronger convergence at the functional network level than at the structural disconnectome level and indicate that lesion-induced hallucinations may be associated with distributed structural disconnection patterns despite consistent functional network involvement.

Disclosures: A.O. Yildirim: None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.22/LL82

Topic: J.03. Anatomical Methods

Title: Brain Circuits Implicated in Apraxia

Authors: *A. PARKER[1], Z. FIORE[1], H. MOORE[1], P. HARRIS[1], C. GERBER[1], H. LARSEN[1], M. GROTENHUIS[1], M. OGAWA[1], J. A. NIELSEN[2];
[1]Dept. of Psychology, [2]Psychology, Brigham Young Univ., Provo, UT

Abstract: This study utilized lesion network mapping (LNM) to investigate neural circuits associated with apraxia, an acquired neurological disorder characterized by an inability to perform movements on command. We analyzed cases of ideomotor apraxia (n=64), the inability to perform learned movements; speech apraxia (n=29), the inability to coordinate facial musculature for speech; and gait apraxia (n=29), the inability to initiate or coordinate walking. Previous studies have linked ideomotor apraxia to parietal cortical regions, speech apraxia to the arcuate fasciculus, and gait apraxia to medial cortical and subcortical brain structures including the cingulate cortex, bilateral pallidum, and left parahippocampal gyrus. However, these disorders have not previously been examined within a unified LNM framework, so it is unknown if they converge on a common network. We conducted a systematic literature review of acquired apraxia case reports in PubMed and Embase. Reports were included if they were published in English, contained clear lesion neuroimaging, and demonstrated a temporal association between lesion onset and apraxia symptoms. A total of 122 cases were included in the study, with lesions stemming from strokes or stroke-mimic disorders (n=82), cancer (n=13), white matter-targeting disorders (n=11), autoimmune disorders (n=10), traumatic brain injuries (n=3), infectious diseases (n=3), genetic disorders (n=1), and other unspecified causes (n=2). Lesions from included cases were manually traced in MNI space using 3D Slicer. We then generated lesion networks by comparing lesion locations with resting-state functional connectivity data from the Brain Genomics Superstruct Project (n=1000). After accounting for specificity, the overlap within 75% of these networks revealed positive associations between apraxia and the body of the corpus callosum, left cingulate gyrus, and left anterior precuneus. These findings suggest that the symptoms of ideomotor, speech, and gait apraxia converge on brain areas devoted to transmitting or integrating sensory and motor information. These areas should be investigated further to understand their potential as diagnostic markers and therapeutic targets. Additionally, the negative association between cerebellar regions and apraxia was not a finding of previous studies and warrants further investigation.

Disclosures: A. Parker: None. **Z. Fiore:** None. **H. Moore:** None. **P. Harris:** None. **C. Gerber:** None. **H. Larsen:** None. **M. Grotenhuis:** None. **M. Ogawa:** None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.23/LL83

Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Neural Networks Implicated in Nystagmus

Authors: *N. THORNTON[1], J. A. NIELSEN[2];
[1]Psychology, Brigham young University, Dept. of Psychology, Provo, NV; [2]Psychology, Brigham Young Univ., Provo, UT

Abstract: Nystagmus is a neurological oculomotor disorder characterized by rapid, repetitive, and involuntary eye movements that impair vision, balance, and spatial orientation. This study aimed to identify common neuroanatomical networks associated with nystagmus researching which brain regions and functional networks are most consistently implicated in its development. To address this question, we conducted a comprehensive literature review of reported cases linking stroke lesions to nystagmus and applied lesion network mapping to these data. This approach enables identification of shared functional networks by analyzing connectivity patterns of lesion sites across individuals. Results revealed a consistent pattern of functional connectivity between lesion locations and the cerebellar flocculus. Although lesion sites varied anatomically, many were part of a shared network involving the flocculus and associated vestibulo-ocular pathways. This convergence suggests that disruption of flocculus-centered circuits plays a central role in the pathophysiology of nystagmus.These findings highlight the importance of cerebellar contributions to oculomotor control and support the flocculus as a key node in maintaining visual stability. Furthermore, the flocculus may represent a promising target for future research, including potential targeted therapeutic interventions.

Disclosures: N. Thornton: None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.24/LL84

Topic: J.03. Anatomical Methods

Support: Brigham Young University Internal Lab Funding

Title: Re-evaluating the neuroanatomical origin of central post-stroke pain via lesion network mapping

Authors: *T. D. CLOWARD[1], J. A. NIELSEN[2];
[1]Brigham Young University, Dept. of Psychology, Provo, UT; [2]Psychology, Brigham Young Univ., Provo, UT

Abstract: A prevalent challenge faced by stroke survivors is the onset of central post-stroke pain (CPSP), characterized by mechanical allodynia, burning or freezing sensations, and shooting pain. Despite its distressing nature, the functional neuroanatomy of CPSP remains incompletely understood, limiting the development of effective treatments, such as targeted neuromodulation. The present study aims to re-evaluate the original CPSP cohort from a foundational study (Boes et al., 2015) using contemporary lesion network mapping (LNM) methodology. Four lesions from the original study were excluded based on strict inclusion criteria, leaving 19 lesions for analysis. Using 3D Slicer, lesions from the cohort MRI data were manually traced voxel-wise onto a standardized MNI template brain and utilized as regions of interest within a normative connectome. Subsequent lesion networks were generated, thresholded ($z \geq 4.7$), and binarized for

both sensitivity and specificity tests, utilizing a large database of control lesions (n=1000). Voxels passing both tests yielded conjunction maps representing the brain regions most highly correlated with CPSP. 95% (18/19) of our lesions showed distinct network conjunction in the ventromedial caudal pons, middle cerebellar peduncles, and cerebellar lobules IX and X. Additionally, 95% conjunction overlap was found at voxels located in the hypothalamus, medial dorsal thalamus, and caudal body of the caudate nucleus. While Boes et al. (2015) highlighted network correlations with the posterior insula, the present study localized CPSP lesion networks to a thalamo-ponto-cerebellar axis. Potential explanations for these differences emerge as certain facets of LNM are considered. While the subjective nature of lesion tracing and MRI resolution quality may each contribute to variable results, greater variability is inherent in the differences between underlying databases. Sensitivity and specificity test results are defined by the diversity of connectome and control lesion data, respectively; thus, variable findings may result from the evolution of this body of data over time. Further LNM analysis is needed in order to validate how the advancement of these massive datasets has redefined CPSP localization. LNM remains a unique tool that addresses key issues inherent in traditional lesion analysis. Complex symptoms such as CPSP can be explained via network analysis despite heterogeneous lesions with little spatial overlap, granting LNM the potential to uniquely refine targeted clinical interventions and enhance patient outcomes.

Disclosures: T.D. Cloward: None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.25/LL85

Topic: J.03. Anatomical Methods

Support: Brigham Young University's John A. Widtsoe Grant

Title: Social Media Use, Sustained Attention, and Episodic Memory in Adults with ADHD

Authors: *R. ENSIGN[1], J. A. NIELSEN[2];
[1]Brigham Young University, Dept. of Psychology, Provo, UT; [2]Psychology, Brigham Young Univ., Provo, UT

Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by dysregulated attention and heightened reward sensitivity, traits that may interact with the algorithmically reinforced structure of short-form video platforms. Much remains unknown about how habitual social media use affects cognition, and whether ADHD status moderates these effects. We recruited healthy young adults (n=125, 75 female; age 18-25, M=20.6) and adults with physician-confirmed ADHD (n=37, 26 female; age 18-25, M=20.5), collecting two weeks of mobile social media use data via the Stay Free app and comparing average daily consumption to performance on the Sustained Attention to Response Task (SART) and Mnemonic Similarity

Task (MST), which quantify sustained attention and episodic memory ability, respectively. Participants were excluded for neurological or psychiatric conditions, history of brain injury, English non-fluency, and colorblindness. In the neurotypical sample, linear regression analyses revealed no association between social media consumption and sustained attention (SART; p=0.969), but a significant association with episodic memory performance (MST; p=0.030). In contrast, our multiple linear regression model did not detect any significant association between social media habits across the two week data collection period and performance on the MST (p=0.483) or SART (p=0.532) in the ADHD sample. Contrary to our hypothesis, habitual social media use did not predict cognitive performance in adults with ADHD, suggesting that the mechanisms linking media consumption to cognition may operate differently in this population. Further research is needed to clarify whether other factors better capture the relationship between social media use and cognitive performance in ADHD. Future research includes the analysis and conclusion of a parallel fMRI study currently being conducted.

Disclosures: R. Ensign: None. **J.A. Nielsen:** None.

Poster

PSTR249: Connectomics

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR249.26/LL86

Topic: J.03. Anatomical Methods

Support: NIH Grant R01MH118257

Title: Fiber pathways of the posteromedial cortex in rhesus macaques: volumetric and connectionist approaches

Authors: *F. AGUILAR ORTEGA[1], E. HAYDAY[2], S. R. HEILBRONNER[1,3];
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Abstract: The posteromedial cortex (PMC), including the posterior cingulate cortex, the precuneus, and retrosplenial cortex, is the central hub of the default mode network (DMN) and has been implicated in self-referential processing, autobiographical memory, and internally directed cognition, functions whose disruption is reflected in altered DMN functional connectivity across psychiatric disorders. PMC functions depend on long-range white matter connections, yet the axonal pathways used by the PMC neurons remain incompletely mapped. Diffusion MRI (dMRI)-derived tractography is the primary tool for mapping structural connectivity non-invasively in humans, but it can miss real connections and detect ones that do not exist. Here, we use tract-tracing, a technique not possible in humans, in the PMC of rhesus macaques (n=4 cases) to characterize PMC fiber pathways using both volumetric and connectionist approaches, with the goal of providing anatomical ground truth for dMRI-derived tractography in macaques and then translating these findings to humans. Our results show that

the cingulum bundle is the dominant conduit for PMC fibers, carrying anteriorly directed projections toward the prefrontal cortex and posteriorly toward the medial temporal lobe via the temporal cingulum. Anteriorly directed fibers fan out near the injection site, consolidate within the cingulum bundle and superior longitudinal fasciculus I through sensorimotor levels, then fan out again within the prefrontal cortex, leaving a largely fiber-free middle zone. Additional projections traverse the corpus callosum, Muratoff's bundle to the caudate, and the extreme capsule to the claustrum and posterior insula. Volumetric and connectionist definitions are well-aligned for the corpus callosum and Muratoff's bundle, but diverge for bundles such as the uncinate fasciculus and frontal occipital fasciculus, where PMC fibers occupy the designated volume without satisfying the connectionist definition. Together, these results characterize PMC fiber bundle usage and identify cases where bundle definitions diverge, providing an anatomical foundation for improving dMRI tractography in macaques and humans.

Disclosures: F. Aguilar Ortega: None. **E. Hayday:** None. **S.R. Heilbronner:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.01/LL87

Topic: J.06. Computation, Modeling, and Simulation

Title: Estimating coding geometry in large neural populations

Authors: *T. LU[1], R. WONG[1], N. HIRATANI[2], H. HU[1], G. J. GOODHILL[3];
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Abstract: Large-scale neural recordings now enable the analysis of population codes in thousands of dimensions, yet these datasets are often trial-limited, providing far fewer repeated trials than recorded neurons. In this high-dimensional regime, finite sampling systematically distorts empirical covariance spectra, signal-noise alignment, and coding subspaces, biasing estimates of coding fidelity, canonical angles, and effective dimensionality. We develop a random matrix theory framework for inferring latent coding geometry from finite-sample observables. Our approach expresses multiple quantities of interest as functionals of a single coding geometry spectrum, enabling a unified description of neural population geometry. We first characterize the forward mapping from latent coding geometry to its high-dimensional, finite-sample distortion, and then invert this mapping to estimate the underlying coding structure from recorded data. We validate the method in controlled simulations and deep neural networks, then apply it to neural population data. In visual cortex recordings during binary sensory discrimination tasks, the framework reveals that conventional decoding analyses can substantially underestimate the fidelity of sensory coding. These results provide a general route for measuring neural coding geometry in the large-scale, data-limited regime increasingly encountered in modern neuroscience.

Disclosures: T. Lu: None. **R. Wong:** None. **N. Hiratani:** None. **H. Hu:** None. **G.J. Goodhill:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.02/LL88

Topic: J.06. Computation, Modeling, and Simulation

Title: Selective neural-BOLD state correspondence reveals a conserved brain-state motif across modalities and species

Authors: *L. HOHEISEL[1], J. KANG[1], F. MANDINO[3], E. BERNAT[2], E. M. LAKE[4], N. XU[1]; [1]Fischell Dept. of Bioengineering, [2]Psychology, Univ. of Maryland, College Park, MD; [4]Radiology and Biomed. Imaging, [3]Yale Univ., New Haven, CT

Abstract: Brain activity is increasingly understood as a dynamic process in which the brain transitions among recurrent neural and hemodynamic states. Although such states have been identified in multiple recording modalities, whether neural and BOLD state dynamics exhibit temporally specific correspondence remains unclear. We analyzed two independent simultaneous EEG-fMRI data in humans (n = 28 and n = 12 respectively). To investigate the biological basis of identified neural-BOLD correspondences, we further extended the analysis framework to simultaneous calcium-fMRI recordings in mice. Humans fMRI data was recorded at 3T (TR = 2 s/2.52 s) and preprocessed using fmriprep , while EEG data underwent artifact removal in EEGLAB , ICA-based cleaning and source localisation. Mouse Ca^{2+}-fMRI recordings included glial and Slc17a7-positive excitatory-neuronal GCaMP-expressing animals. Calcium and BOLD signals were mapped to a common Allen CCFv3 space to enable comparison of state dynamics across matched cortical regions. Hidden Markov Models (HMMs) were applied separately to each modality and to band-limited neural signals. We quantified temporal correspondence between cross-frequency neural-state configurations and BOLD states using lagged co-occurrence analyses, circular-shift permutation testing, and cluster-based statistics. We further examined associations between identified neural-BOLD states and large-scale neuromodulatory receptor systems and investigated analogous state correspondence in cell-type-specific calcium-fMRI recordings. Neural and BOLD state repertoires exhibited limited spatial and temporal correspondence overall. However, we identified a reproducible cross-frequency neural-state configuration that selectively co-occurred with a single BOLD state characterized by prominent negative engagement of the default mode and frontoparietal networks. This state exhibited significant temporal coupling and elevated occurrence probability around neural-state onset. Components of the co-occurring state exhibited significant associations with large-scale neuromodulatory receptor systems. Preliminary calcium-fMRI analyses revealed analogous state correspondence in glial calcium recordings, motivating ongoing investigation of the cellular basis of neural-BOLD state coupling. Together, these findings identify a biologically specific neural-BOLD state and suggest that interactions among neural, neuromodulatory, and

neurovascular processes may contribute to correspondence between brain-state dynamics across modalities and species.

Disclosures: L. Hoheisel: None. **J. Kang:** None. **F. Mandino:** None. **E. Bernat:** None. **E.M. Lake:** None. **N. Xu:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.03/LL89

Topic: J.06. Computation, Modeling, and Simulation

Title: A BOLD forward model in macaque M1-PMd preserves the time-averaged communication subspace but loses its fast reconfiguration

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Abstract: fMRI is a non-invasive tool for human brain communication, but BOLD signal is an indirect proxy. It reflects synaptic input rather than spike output and low-pass filters neural dynamics below ~0.15 Hz (to ~0.75 Hz with fast fMRI). Meanwhile, communication is increasingly described via low-dimensional spike-level population geometry, the communication subspace, with human frontal-motor evidence from intracranial recordings. This account has not been connected to non-invasive signals. To understand what BOLD connectivity can and cannot say about communication, we characterize how the neural-to-BOLD transform alters subspace geometry.We applied a temporal forward model of the BOLD transform to a measured macaque M1-dorsal-premotor (PMd) communication subspace during reaching (DANDI 000070; two sessions, one animal), computed in the M1-to-PMd direction. Subspace dimensionality was set by cross-validated reduced-rank regression (the simplest rank within one SEM of the best CV performance), with a within-area guardrail. We convolved population activity with hemodynamic response functions, from the canonical HRF to faster empirical responses, and downsampled across repetition times. Collapse was quantified as rotation-spanned dimensionality (participation ratio of the union of sub-window subspaces), as excess over a resample-matched floor, with inert-scalar and ±1 s inter-areal-lag controls.The movement-epoch subspace rotated within the window (mean principal angle ~71 deg vs a ~42 deg same-window floor; within-session permutation $p<0.001$), reorienting faster than the ~0.15 Hz canonical hemodynamic passband. In session 0912 the M1-to-PMd subspace was rank-4 during movement and rank-1 during delay. With rotation, the spanned dimensionality inflates from 4 to ~7.4. The transform strips rotation, collapsing it to the ~4-dimensional window-integral floor (~99% of rotational excess removed); replicated in a second session. The collapse held regardless of HRF shape and was not rescued by faster TR (0.1-3.0 s). A ±1 s inter-areal lag produced no spurious dimensionality on real or area-shuffled data.Temporal integration reduced the rotation-spanned dimensionality to the rank-4 window-integral and no further. The transform preserves the time-

averaged subspace but not the faster reorientation. The model is temporal-only; spatial (voxel) pooling cannot increase rank, so rank-4 is an upper bound on what BOLD preserves. It predicts human M1-PMd BOLD connectivity is low-rank, at most the time-integrated subspace, and not improved by faster TR.

Disclosures: J. Cho: A. Employment/Salary (full or part-time):; Accenture.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.04/LL90

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH NIDA-R34-DA061924

Title: Topological data analysis reveals transient neural states in ferrets during naturalistic social interaction

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Abstract: Traditional investigations on the neural underpinnings of social interaction relied on repetitive laboratory tasks. Recent studies have turned to more naturalistic settings, where brain oscillations were found to synchronize across animals. However, such inter-brain synchronization was primarily studied using time-averaged methods, thereby losing much of the complexity of inter-brain dynamics. Moreover, little is known about inter-brain dynamics beyond synchronization. A known barrier is the lack of data analysis tools capable of characterizing high-dimensional neural activity in finer detail without gross averaging. A potential solution lies with Topological Data Analysis (TDA), where computational tools are designed to characterize the “shape” of high-dimensional data. This work leverages a newly developed TDA tool, Temporal Mapper, which represents complex neural dynamics as transition networks in which nodes represent stable states and edges represent transitions between states. Here, we investigated the organization of diverse dyadic brain states by applying Temporal Mapper on an existing electrophysiology dataset recorded from freely interacting ferrets. We chose ferrets as a model because they have strong social-cognitive skills, and their theta (4-8 Hz) and alpha (8-12 Hz) oscillations are homologous to those of humans. Importantly, alpha and theta oscillations have been observed to mediate inter-brain synchronization in humans. Our

dataset consists of simultaneous electrophysiology recording in the posterior parietal cortex (PPC) (5 sessions) or the premotor cortex (PMC) (5 sessions) of both animals. Using Temporal Mapper, we constructed transition networks from spectrograms of the local field potential combined from both animals, where nodes represent stable dyadic neural oscillatory states. Our preliminary analysis showed that dyadic PPC oscillatory states are significantly smaller during active social interaction than during non-social activities within PPC ($p<0.05$) and marginally significant within PMC ($p=0.09$). This finding suggests that dyadic neural oscillatory states underlying active social interaction are less stable than non-social activities. Such neural dynamics align with previously reported behavioral dynamics of the same data, where dyadic postural states were less stable during active social interaction. Alignment between neural and behavioral network features provides a unified representation for identifying mechanistic links between brain and behavior. In future work, we will develop a computational toolbox that systematically maps between neural and behavioral transition networks.

Disclosures: J. Reiling: None. **G. Dumas:** None. **N. Padilla-Coreano:** None. **F. Frohlich:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of North Carolina, Chapel Hill, Academic Press, Flavio Labs LLC, Qortical Clinical Partners Inc.. F. Consulting Fees (e.g., advisory boards); Electromedical Products International (EPI), Inselspital, Bern University Hospital. **M. Zhang:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.05/LL91

Topic: J.06. Computation, Modeling, and Simulation

Support: the National Science Foundation of China (32271430, 62361166631)
the Operating Funds for Multimodality Imaging Center of the HFCNS Institute of Artificial Intelligence

Title: Connectome-scale self-supervised representation learning reveals neuronal organization beyond canonical labels

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Abstract: Dense electron-microscopy connectomes provide synaptic-resolution maps of neuronal structure and wiring, but learning scalable representations that integrate structure and connectivity for connectome discovery with minimal human intervention remains difficult. Here we present a self-supervised framework for structure-connectivity representation learning in dense connectomes. A hierarchical graph neural network with skeleton decomposition enables

contrastive learning from finely sampled FlyWire neuronal skeletons, showing that fine skeletons preserve substantially richer identity information than coarse representations. Coordinate-free topology reduces developmental and geometric confounds, improving clustering and label-efficient inference. We then use learned structural embeddings as continuous descriptors of synaptic partners to construct structure-driven connectivity representations, improving subtype discrimination without predefined partner-type labels. Iterative multi-hop learning further reveals higher-order organization, including hemispheric connectivity lateralization and connectivity-defined subgroups. Attention analysis links these differences to specific synaptic partners. Together, these results establish a self-supervised and scalable framework for discovering neuronal identity and connectome organization in a large-scale dense connectome.

Disclosures: T. Shi: None. **R. Zhang:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.06/LL92

Topic: J.06. Computation, Modeling, and Simulation

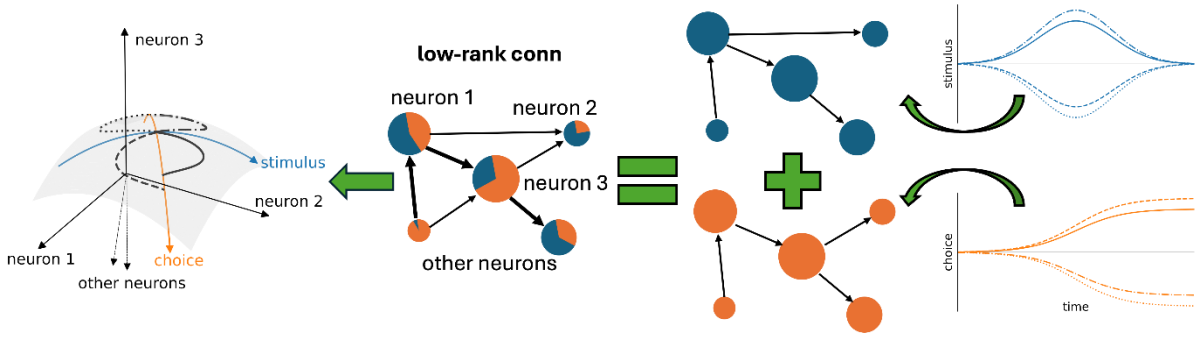
Support: Alfred P. Sloan Foundation (CL and AW)
DARPA HR0011-25-3-0139 (CL and AW)
NIH/NINDS Award U01NS131810 (CL and AW)

Title: Disentangling time-varying neural latent dynamics and circuit-level connectivity with subspace-attention gating

Authors: *C. LI[1], K. LU[2], Y.-S. SU[1], J. KE[1], C. RODGERS[3], R. C. LIU[2], A. WU[1];
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Abstract: Understanding when task variables such as stimulus and choice are encoded in population activity requires single-trial analysis without fixed temporal alignment across trials. Existing latent variable models assume stationary subspaces or trial-wise temporal rescaling, obscuring within- and across-trial timing variability. We developed a subspace-attention gated latent dynamical model (SAG-LDM) with per-time-point encoder-decoder mappings and label-specific temporal attention that (1) separates label-specific subspaces, (2) identifies when each subspace rises and falls on every trial, (3) maps time-varying contributions of individual neurons to each subspace, and (4) infers directed connectivity mediating message flow across subspaces (Fig. 1). In two datasets, SAG-LDM revealed matching structure in latent dynamics and connectivity. During a head-fixed whisker task (S1, 14 neurons), stimulus attention peaked at first contact ($t=10.091$, $p<0.001$) before choice ($t=5.133$, $p<0.001$); stimulus coding was more transient than choice (IQR: 0.247 ± 0.367 vs. 0.371 ± 0.307 s). Correct trials showed sequential stimulus-to-choice trajectories and recruitment of stimulus-exclusive, relay, and choice-exclusive

units; error trials showed choice attention before first contact and weakened sensory-to-relay coupling. In a freely moving auditory T-maze, mice learned over 8 days to choose the sound-cued arm, and SAG-LDM separated stimulus, choice, and memory subspaces despite variable trial length. On day 1, high memory attention before sound onset translated into elevated choice attention after onset, consistent with win-stay-lose-switch behavior. On day 8, memory attention stayed weak; post-onset stimulus attention rose and drove choice attention, indicating sound-cued, stimulus-based decisions. Together, SAG-LDM disentangles when task information emerges on single trials, maps neuron routing across subspaces, and tracks how connectivity reorganizes with learning and changing decision strategy.



Disclosures: C. Li: A. Employment/Salary (full or part-time):; Meta Platforms Inc.. **K. Lu:** None. **Y. Su:** None. **J. Ke:** None. **C. Rodgers:** None. **R.C. Liu:** None. **A. Wu:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.07/LL93

Topic: J.06. Computation, Modeling, and Simulation

Support: Howard Hughes Medical Institute
European Research Council

Title: Embodied connectome-constrained inference of Drosophila neural activity from behavior

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Seattle, WA; [10]Mechanistic Cognitive Neurosci., Janelia Res. Campus, Ashburn, VA; [11]Howard Hughes Med. Inst., Ashburn, VA

Abstract: Animal behavior arises from feedback loops between the brain and the body. In Drosophila, we now have complete connectomes of the nervous system and detailed physics simulations of the body [Vaxenburg 2025]. Connecting them requires knowing which neurons drive which muscles and read out which sensors, a correspondence the connectome alone does not provide. We therefore curate a dataset mapping individual motor neurons to the muscles they actuate and sensory neurons to the peripheral structures they innervate, linking VNC cell types to the physical body. Building on this mapping, we construct an embodied, connectome-constrained simulation of the fly ventral nerve cord (VNC) coupled to the body. A MuJoCo body simulation is controlled by a network of VNC neurons with conductance-based voltage dynamics and trainable neuronal and synaptic parameters. Motor neurons drive Hill-type muscles; proprioceptors such as chordotonal organs, campaniform sensilla, hair plates, and bristles transduce the resulting movement back into sensory input. Extending the connectome-constrained latent variable model of [Mi 2022] to an embodied motor system, we treat the membrane voltages of all VNC neurons as latent variables whose dynamics are generated by the biophysical simulation that serves as the generative model. An inference network maps observed behavior to an approximate posterior over these latents. Trained on a diverse database of whole-body behavioral measurements, the model yields a full-VNC estimate of neural activity for each behavior, validated against held-out behaviors and published functional imaging of identified VNC cell types. This lets us infer the activity of tens of thousands of never-recorded neurons and predict how VNC circuits transform commands and feedback into coordinated movement.

Disclosures: J. Ellis-Joyce: None. **M.I. Eberle:** None. **G. Both:** None. **M. McGill:** None. **I. siwanowicz:** None. **R. Vaxenburg:** None. **S. Tata Ramalingasetty:** None. **A. Bates:** None. **J.I. Ispizua:** None. **E. Abe:** None. **J. Yan:** None. **R. Othayoth:** None. **M. Pals:** None. **A.W. Azevedo:** None. **J. Tuthill:** None. **B.W. Brunton:** None. **W. Korff:** None. **R. Johnson:** None. **J.H. Macke:** None. **S. Turaga:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.08/LL94

Topic: J.06. Computation, Modeling, and Simulation

Support: Swartz Foundation
NSF Grant 2350329
NIH Grant R34DA059718

Title: Disentangling condition-specific neural dynamics with mixtures of linear dynamical systems

Authors: *L. GONG[1], S. SAXENA[2];
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Abstract: Neural activity often varies across task conditions, behavioral contexts, and trials. Thus, an important question is to determine whether these variations reflect only noise or whether they reveal distinct latent dynamic modes that support different computations. Dynamical systems models provide interpretable descriptions of the high-dimensional neural population activity, but we still lack systematic approaches for investigating the potential dynamical modes across conditions and trials. Utilizing a single dynamical system model on all neural data, such as a linear dynamical system (LDS), will usually collapse condition-specific structures across trials; switching-based LDSs mainly capture regime changes within a trajectory; and supervised conditional LDS approaches require explicitly known task labels or condition variables. Motivated by these, we develop an unsupervised and interpretable framework to identify condition-specific dynamical components directly from large-scale neural and behavioral recordings.Our model is a Mixture of Linear Dynamical Systems (MoLDS), in which each neural trial is assumed to generate from one of several latent LDS components. To learn the reliable MoLDS model for noisy and high-dimensional neural data, we design a hybrid learning strategy that combines spectral initialization via subspace system identification methods and likelihood-based Expectation-Maximization (EM) refinement. The initialization estimates candidate dynamical components from the collective neural data, and Kalman-EM iteratively refines latent states, LDS component parameters, and mixture weights for more accurate and reliable models. This provides an unsupervised and principled approach for discovering underlying dynamical modes without imposing any condition labels.We apply the MoLDS model to different neural datasets. In the somatosensory recordings during a monkey's reaching task with multiple directions, the model identifies direction-specific dynamical components across trials. These components recover structure consistent with reach direction and supervised per-direction LDS results, suggesting that a small set of dynamical modes can organize neural responses across movements. Applying this model to neural data from a decision-making task, we infer dynamical components that reveal distinct evidence-integration dynamics associated with different stimuli and choices. These results demonstrate that MoLDS provides an interpretable framework for capturing condition-specific neural dynamics, with the learning scheme providing a stable and principled approach for MoLDS learning on neural data.

Disclosures: L. Gong: None. **S. Saxena:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.09/LL95

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH grant 1R01MH143055

Title: Data-driven inference of pharmacokinetic modulation of neural dynamics

Authors: *Z. YU[1], B. A. PALANCA[3], S. CHING[2];
[1]Washington Univ. in St. Louis, St. Louis, MO; [2]Electrical and Systems Engin., Washington Univ. in St. Louis, Saint Louis, MO; [3]Anesthesiol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: A feature of computational modeling of neural circuits is the opportunity to infer and predict the effects of extrinsic modulation on brain mechanisms, as a means toward scientific and clinical endpoints. This work introduces a data-driven system identification approach to construct personalized state-space models of neural dynamics modulated by extrinsic pharmacologic agonists. Our goal is to enable the joint modeling of neural circuit mechanisms at the population scale, alongside pharmacokinetics, thus capturing an aspect of brain-body interaction. We developed a Hopfield-inspired nonlinear state-space model that characterizes the generative dynamics of excitatory-inhibitory (E-I) circuits. A pharmacokinetic stage is added, such that drug-dependent parametric modulation can be enacted via an inferred effect-site concentration. We develop a computational optimization framework to estimate all parameters (neural, pharmacokinetic) in this modeling scheme from indirect measurement, specifically EEG. Models are obtained on the basis of single-subject recordings, hence individualized. Identified models are then forward-simulated to generate and analyze the reconstructed neural dynamics. To demonstrate validity of this modeling framework, we apply it to EEG recordings during Propofol anesthesia, which are electrophysiologically well-characterized. We show that the modeling framework is able to recapitulate known dynamical regimes, such as alpha- and delta-band activity, at expected dose levels. The model indicates that such oscillatory regimes are associated with limit-cycle structures in the state space, suggestive of a Hopf bifurcation mechanism, again consistent with extant hypothesis regarding Propofol's circuit-level effects. Together, these results demonstrate that data-driven biophysical modeling can bridge electrophysiology and pharmacokinetics, offering a principled framework for studying the generative mechanisms underlying pharmacologically modulated neural dynamics.

Disclosures: Z. Yu: None. **B.A. Palanca:** None. **S. Ching:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.10/LL96

Topic: J.06. Computation, Modeling, and Simulation

Support: Incentive Research Projects
(to TT) RIKEN TRIP initiative (RIKEN Quantum)
JST CREST Grant No. JPMJCR23N2
JSPS KAKENHI Grant No. JP25K24466

Title: Psychologically anchored fNIRS brain-state discovery during the rubber hand illusion

Authors: *H. WANG[1], T. TOYOIZUMI[1,2];
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Abstract: Dynamic brain-state discovery aims to identify recurrent neural patterns over time, yet most approaches learn exclusively from neural signals and incorporate stable psychological structure only after states have been discovered. This overlooks how psychologically meaningful structure may shape the state-discovery process itself. Here, we present a psychologically anchored framework for dynamic brain-state discovery by reanalyzing Ferri et al.'s touch-expectation rubber hand illusion (RHI) dataset, which includes functional near-infrared spectroscopy (fNIRS) oxygenated-hemoglobin recordings from 24 cortical channels and multi-item embodiment questionnaires in 15 participants. The model uses adaptive graph neural networks (GNNs) to model inter-regional interactions and self-supervised contrastive predictive learning to learn latent neural embeddings. Questionnaire responses are represented as soft psychological profiles and introduced as training-time constraints at feature, node, and graph levels, biasing the model toward neural patterns that are both recurrent in the signal and behaviorally meaningful. Questionnaire-guided multiscale alignment linked subjective embodiment dimensions to distributed cortical network patterns while improving the learned fNIRS embedding space. Rather than reducing each trial to a single behavioral score, the resulting embeddings identified questionnaire-related channel patterns whose structure depended on anatomically consistent cortical organization. Spatial misalignment and channel averaging both reduced the overlap of contributing channels, indicating that the questionnaire-to-channel mapping depended on preserved anatomical correspondence. Time averaging also weakened this mapping, whereas temporal reordering largely preserved the global channel pattern, suggesting a stronger dependence on spatial network organization than on exact temporal order. These effects were accompanied by improved embedding separability relative to an unguided contrastive GNN baseline, and clustering remained stable across random seeds. These findings suggest that subjective body ownership during RHI is reflected in spatially organized cortical network dynamics, offering a data-driven bridge between post hoc embodiment reports and time-resolved neural state discovery.

Disclosures: H. Wang: None. **T. toyoizumi:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.11/MM1

Topic: J.06. Computation, Modeling, and Simulation

Title: An LSTM Model of the Synchronization-Continuation Task: Emergent Timing Dynamics and Neural Geometry

Authors: *M. AGUIRRE[1], O. PEREZ[2];
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Abstract: The synchronization-continuation task (SCT) has been used to study the neural basis of rhythmic timing in rhesus macaques (Macaca mulatta), with recordings from the medial premotor cortex (MPC), particularly the Supplementary Motor Area (SMA), revealing a rich repertoire of interval-selective and phase-tracking neural responses (Merchant et al.). Here we present a computational model of the SCT based on a Long Short-Term Memory (LSTM) network trained to reproduce the temporal structure of the task across a range of inter-onset intervals and tested for generalization across a broader range of time intervals (200ms - 1500ms). The network receives rhythmic pulse sequences paired with a scalar period context cue and is trained to generate a continuous oscillation at the corresponding frequency, capturing both the synchronization and stimulus-free continuation phases of the task. The LSTM successfully learns the task and generalizes across the full range of tested intervals. Analysis of the network's internal representations reveals activation patterns that qualitatively resemble those observed in primate premotor neurons: individual units exhibit event-locked responses at stimulus onsets, phase-tracking dynamics consistent with learned beat-period oscillators, and activation patterns suggestive of traveling bump-like dynamics in which sequential unit recruitment propagates across the network in a manner reminiscent of the moving bumps of neural activity reported in MPC populations. Principal component analysis of the hidden state trajectories yields approximately circular geometries whose radii scale with inter-onset interval, recapitulating a hallmark feature of the neural population dynamics reported in SMA recordings. These findings suggest that recurrent network dynamics are sufficient to account for key computational properties of biological interval timing, and motivate further use of the model as a tool for generating hypotheses about the preparatory and anticipatory mechanisms that enable successful rhythmic synchronization in the primate brain.

Disclosures: M. Aguirre: None. **O. Perez:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.12/MM2

Topic: J.06. Computation, Modeling, and Simulation

Title: Encoding-model analysis links neuronal reliability to heterogeneous behavioral state modulation in mouse primary visual cortex

Authors: *H. HU[1], N. DONOVAN[2], R. ABBASI-ASL[3];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]UCSF, San Francisco, CA, ; [3]Univ. of California, San Francisco, Walnut Creek, CA.

Abstract: The MICrONS functional connectomics dataset is a landmark dataset that records the activity of tens of thousands of neurons in mouse visual cortex during natural movie viewing (The MICrONS Consortium, 2025). These data are paired with simultaneous behavioral measurements and synaptic connectivity. We sought to understand how the behavioral information relates to the ongoing visual cortical activity. To do so, we built a four-module encoding model for mouse primary visual cortex (V1): a 2+1D CNN core capturing temporal and visual features, a feature-shifting module that reconstructs the feature map from gaze position, a per-neuron Gaussian readout learning where each neuron looks, and a behavioral modulation multilayer perceptron (MLP) receiving treadmill velocity and pupil dilation. This setup isolates how each module, specifically behavior, contributes to predicted activity. The model achieves a best single scan Pearson correlation of 0.229 and CCnorm of 0.6126 (a noise-corrected performance metric dividing the model's raw correlation by neurons' reliability ceiling). The behavioral MLP applies two learned, per-neuron operations — a multiplicative gain that scales the prediction and an additive shift that offsets it (response = gain × prediction + shift). Our core finding relates the learned gain and shift to each neuron's oracle score, a measure of response consistency across repeated stimuli. At low arousal, gain modulation is heterogeneous: high-oracle neurons show larger gain; at high arousal, gain converges toward uniformity. Low-oracle neurons show a steeper gain change as treadmill velocity increases. Moreover, across all treadmill velocities, lower-oracle neurons show significantly higher shift modulation. Our interpretation is that different neurons have different ratios of how stimulus driven and non-stimulus driven (behavioral) components affect their final response. At low arousal, high oracle neurons are more stimulus driven, thus having more visually driven response fraction. At high arousal states, neurons become more stimulus driven in general, and the low oracles catches up the high oracles. The shift term adds the internally-driven activity that gain has excluded to the final response. Consequently, the result proposes a specific, testable mechanism for behavioral modulation: rather than uniformly amplifying activity, behavioral state reweights how much of each neuron's response is stimulus-driven versus internally generated, and it reframes the oracle score not only as a static index of neuron reliability but also as a measure of how invariant a neuron's stimulus-driven activity is to behavioral state.

Disclosures: H. Hu: None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.13/MM3

Topic: J.06. Computation, Modeling, and Simulation

Support: The Center for Curiosity

Title: Subacute effects of a DMT and harmine meditation retreat on the brain's control energy landscape are subtle, network specific, and timescale specific

Authors: *I. LLANO ARISTIZABAL[1], K. HEFTER[2], S. S. KULKARNI[3], D. TAMIR[5], D. S. BASSETT[4];
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Abstract: By modeling the brain as a controllable structural network, we estimate the control energy (CE) needed to activate functional states. States that are easy to reach require low CE, while harder ones require higher. Psychedelics are thought to "flatten" this energy landscape, broadening the available states, which may underlie breakthroughs reported in psychedelic therapy. Anecdotal reports describe an “afterglow” that persists after the acute effects and improves outcomes, but it is unclear whether this reflects a lasting energy reorganization. This exploratory study uses rs-fMRI from a randomized, double-blind, placebo-controlled study (N = 39, 19 DMT + harmine ayahuasca analog (verum), 20 placebo) scanned before and after a three-day meditation retreat. We compute minimum CE on a group Human Connectome Project (HCP) structural connectome in two stabilization regimes, one that emphasizes longer timescales and one that emphasizes shorter, and repeat at Schaefer 100, 200, and 400 for robustness. Globally, CE returns to baseline in both groups, so any afterglow is unlikely to be global, and instead points to network-specific change. These effects track intrinsic timescales. Under the longer timescale, the central executive network (CEN) shows an FDR-BH post-retreat CE increase in verum. CE and functional connectivity are distinct, but one plausible reading is that a higher cost to drive the CEN reflects the reduced within-network connectivity reported subacutely after psilocybin. A default mode trend (not surviving FDR) appears in both conditions, likely a meditation rather than drug effect. Under the shorter timescale, the visual network shows an FDR-BH CE decrease in verum, consistent with reduced dynamical demand on a region dense in receptors that are acutely engaged by DMT. We also examine rare states (top 10th percentile information content), where psychedelics may act preferentially. The relationship between CE entering and leaving each state creates a slope describing the local landscape, with values < 1 marking states easier to leave than to enter. A linear mixed effects model under the longer timescale shows a significant session by condition interaction in this slope, shifting more in verum, a modest preferential reshaping given between-subject heterogeneity. Effects reproduce in male and female subgroups with no significant sex differences. The two stabilizations act as a timescale lens, separating which network effects emerge. Overall, these exploratory findings point to network- and timescale-specific rather than global CE changes in the afterglow window, though they are small and heterogeneous and need confirmation in larger samples.

Disclosures: I. Llano Aristizabal: 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 Assistant at the Bassett Lab, The Center for Curiosity. **K. Hefter:** None. **S.S. Kulkarni:** None. **D. Tamir:** None. **D.S. Bassett:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.14/MM4

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH R01NS39600
NSF 2424326
DOE GAINS

Title: Neuron-type effective connectivity of the rodent hippocampal formation by data-driven neural mass modeling

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Abstract: The mammalian hippocampal formation is a canonical system for linking cellular diversity to circuit computation, but multiscale neuron-type models require quantitative integration of cell-specific anatomical, electrophysiological, and synaptic data. We report a neuron-type-level effective-connectivity implementation that extends prior conceptual work by combining a synaptic-population weight matrix with postsynaptic input-output functions. For each directed presynaptic-postsynaptic neuron-type pair, we computed synaptic-population weight from five biological factors extracted from Hippocampome.org: presynaptic census, directed connection probability, synaptic conductance, driving force, and synaptic decay time constant. We estimated postsynaptic gain from neuron-type firing-rate/current (f-I) curves generated with neuron-type-specific Izhikevich models constrained by database-derived minimum inter-spike intervals. This approach links intrinsic excitability to circuit-level responsiveness while preventing unrealistically high firing-rates. We applied this framework to 85 neuron types from dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex, representing ~90% of the total neuron count of the hippocampal formation. The resulting directed graph contained 1641 edges (21.19% density): 352 excitatory-to-inhibitory (E-I), 382 E-E, 171 I-E, and 736 I-I. Dynamic simulations temporally evolve a neuron type-specific population activity vector by multiplying it with the synaptic matrix and transforming the result through f-I lookup tables. Such neural mass representation can be combined with detailed spiking models into multiscale simulations. Furthermore, we define effective connectivity as the product of synaptic-population weights by linearized postsynaptic gains. The resultant matrix enables neuron type-specific, graph-theoretic, effective connectivity analyses of the hippocampal circuit.

Disclosures: J. Santa Cruz Yabarrena: None. **G.A. Ascoli:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.15/MM5

Topic: J.06. Computation, Modeling, and Simulation

Support: NSF 2350329

Title: Learning Interpretable Switching Dynamics in Shared Neural-Behavioral Latent Space

Authors: *Y. ZHANG[1], R. L. OREN[1], M. J. HIGLEY[4], J. A. CARDIN[2], A. K. CHURCHLAND[5], S. SAXENA[3];
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Abstract: Modern recording technologies enable simultaneous measurement of high-dimensional neural activity and rich behavioral variables, creating both an opportunity and a modeling challenge: identifying the shared latent structure that mediates the brain-behavior relationship and the underlying dynamics through which it evolves across behavioral states. Existing approaches focus on different parts of this challenge: shared representation learning methods identify neural-behavioral subspaces but typically do not model dynamical structure, while dynamical models capture temporal variation and discrete state transitions in neural activity, but do not explicitly disentangle shared neural-behavioral structure from modality-specific variability. We introduce Switching Shared Latent Dynamics (SSLD), a unified framework that learns a latent representation shared between neural activity and behavior and endows this shared space with nonlinear switching recurrent dynamics to reflect the hypothesis that behaviorally relevant neural representations exhibit structured dynamical changes across behavioral states. Complementary private latent variables capture modality-specific variability, providing a window into neural activity that does not directly interact with behavior. We evaluate SSLD on a simulated dataset and four diverse experimental datasets spanning species, brain regions, and recording modalities: monkey motor and premotor cortex during reaching, somatosensory cortex during a bump task, widefield calcium imaging across mouse dorsal cortex during (a) self-initiated decision-making and (b) spontaneous movements. Across all four datasets, SSLD accurately reconstructs neural and behavioral signals, recovers discrete states in the dynamics that align with experimentally defined behavioral epochs, and isolates behaviorally-relevant neural information in the shared latent while preserving private neural variability. Ablations confirm that shared representation learning, behavioral supervision, and switching dynamics each contribute to performance. SSLD offers an interpretable approach to modeling shared neural-behavioral dynamics that complements ongoing efforts toward foundation models for neuroscience.

Disclosures: Y. Zhang: None. **R.L. Oren:** None. **M.J. Higley:** None. **J.A. Cardin:** None. **A.K. Churchland:** None. **S. Saxena:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.16/MM6

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH BRAIN RF1NS128896
NIBIB T32EB025816

Title: Real-Time Bidirectional Closed-Loop Adaptive Control of Neural Populations Using a Latent State-Space Framework in Awake Mice

Authors: *J. HA[1,2], D. A. WEISS[2], A. M. F. BORSA[3], G. B. STANLEY[2];
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Abstract: Causal dissection of neural circuits requires precise manipulation of population activity patterns across distributed networks. While closed-loop optogenetic approaches can adapt stimulation based on ongoing neural activity, most existing methods remain limited to low-dimensional or single-input single-output control schemes, constraining their ability to regulate complex population dynamics. Here, we developed a real-time multi-input multi-output (MIMO) adaptive control framework for bidirectional steering of latent neural population activity in awake mice. We validated this platform across multiple brain regions, including the sensory thalamus, primary somatosensory cortex, and hippocampus. To enable bidirectional optical control, we expressed the dual-wavelength opsin somBiPOLES in target brain regions and recorded multichannel spiking activity using 32-channel laminar probes. Population activity was projected into a low-dimensional latent space using Gaussian Linear Dynamical System (GLDS) models fit from white-noise perturbation experiments. During online experiments, latent states were recursively estimated in real time using an augmented Kalman filter implemented within the Real-Time eXperiment Interface (RTXI), enabling adaptive compensation for ongoing network fluctuations with loop latencies below 10 ms. Control signals were generated using a Linear Quadratic Regulator (LQR) to dynamically modulate orange-light excitation and blue-light inhibition relative to target neural states. Preliminary results demonstrate rapid and reliable bidirectional modulation of neuronal firing across multiple simultaneously recorded channels. Compared to static open-loop stimulation, adaptive closed-loop control more stably maintained target activity patterns and reduced variability arising from spontaneous circuit fluctuations, as measured by tracking error and Fano factor. These experiments establish a scalable framework for real-time control of latent neural population dynamics across distributed circuits. In addition to applications in brain-machine interfaces and adaptive neuromodulation, this approach may provide a powerful tool for probing corticothalamic feedback mechanisms, including layer 6 corticothalamic (L6CT) modulation of thalamic sensory processing.

Disclosures: J. Ha: None. **D.A. Weiss:** None. **A.M.F. Borsa:** None. **G.B. Stanley:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.17/MM7

Topic: J.06. Computation, Modeling, and Simulation

Support: University of Maryland startup funds to Nan Xu.

Title: Stimulus-anchored autoregression reveals shared and individualized movie-evoked fMRI trajectories

Authors: J. ZHAO[1], *N. XU[2];
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Abstract: Predicting functional MRI (fMRI) responses to continuous naturalistic video provides a framework for studying how the human brain transforms dynamic visual information into neural trajectories and how these stimulus-locked responses generalize across individuals. A major challenge is separating stimulus-driven activity that is shared across observers from subject-specific temporal dynamics that vary across individuals. We studied cross-subject video-to-fMRI prediction using the Human Connectome Project 7T movie-watching dataset. After excluding incomplete recordings, 159 participants (60 male, 99 female) were analyzed; 111 subjects were used for training/validation and 48 held-out subjects for testing. fMRI time series were extracted with the Schaefer-Yeo 400-parcel cortical atlas, and visual features were extracted from four movie clips using a pretrained CLIP encoder at 1 frame/s. We compared latent prediction, stimulus-only ridge regression, and history-aware autoregressive neural sequence models under recursive rollout. We then developed a stimulus-anchored autoregressive framework that decomposes prediction into a stable stimulus-derived reference trajectory and a history-aware dynamic predictor, combining them with a reliability-controlled fusion coefficient. This constrains the closed-loop influence of predicted history while preserving useful subject-specific temporal corrections. Across four movie clips, ridge-based anchored fusion improved held-out-subject prediction over stimulus-only ridge regression, with mean correlation increasing from 35.98% to 39.39%, 39.47% to 42.53%, 33.61% to 36.03%, and 37.28% to 41.12% for Movies 1-4. Region-wise analyses revealed the strongest predictability within visual and visual-association networks, suggesting that stimulus-driven representations are most consistently shared across individuals in sensory and higher-order visual systems. Horizon-dependent experiments showed that anchoring prevented catastrophic autoregressive drift by falling back toward the stable stimulus-driven reference when history became unreliable. These findings suggest that naturalistic brain responses contain both stable stimulus-driven components shared across individuals and subject-specific temporal dynamics. Explicitly separating these components improves cross-subject prediction and provides a framework for studying how common and individualized neural representations emerge during continuous sensory experience.

Disclosures: J. Zhao: None. **N. Xu:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.18/MM8

Topic: J.06. Computation, Modeling, and Simulation

Title: Neural Codes for Timing and Context Generalization During Rhythmic Tapping in SMA, PFC, and Putamen

Authors: *O. PEREZ[1], H. MERCHANT[2];
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Abstract: The processing of millisecond-scale temporal information is crucial for motor coordination, language, rhythms, and other higher cognitive abilities. Previous studies have indicated that the supplementary motor area, prefrontal cortex, and putamen play critical roles in time perception through various mechanisms. In this work, we present original observations from electrophysiological recordings obtained in macaques performing a multi-interval synchronization-continuation task under varying contextual demands, including changes in sensory modality and serial order. These recordings revealed interval tuning, ramping activity, and neuronal sequences across all three regions. Using clustering algorithms, we identified distinct populations of interval-tuned neurons with varied temporal dynamics. Notably, SMA neurons exhibited robust generalization of temporal representations across different modalities and task structures, maintaining consistent timing codes despite contextual changes, whereas PFC and putamen showed more context-dependent dynamics, suggesting specialized but complementary roles in flexible timing behavior. To integrate these observations, we developed a recurrent neural network model based on firing rates capable of reproducing the observed neuronal response patterns. The model captures the electrophysiological characteristics of each region and simulates how recurrent connectivity may support both stable and adaptive temporal coding. Our results support the hypothesis that while SMA, PFC, and putamen all contribute to time representation, the SMA serves as a central node for context-general temporal processing. This insight enhances our understanding of the neural architecture underlying flexible timing and its relevance to cognitive and motor functions.

Disclosures: O. Perez: None. **H. Merchant:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.19/MM9

Topic: J.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant Number 25KJ1662
JSPS KAKENHI Grant Number JP24K15104
AMED-CREST 26gm1510005s0206

Title: Self-organization of high-dimensional geometry of neural activity in culture

Authors: *A. NAKAMUTA, J.-N. TERAMAE;
Kyoto Univ., Kyoto, Japan

Abstract: Large-scale recordings have revealed that spontaneous population activity in the brain exhibits scale-free high-dimensional structure, but whether this structure is self-organized during development or acquired through sensory experience remains unclear. To isolate intrinsic self-organization from prior sensory learning, we recorded spontaneous spiking activity from dissociated E18 rat cortical neurons cultured on high-density multi-electrode arrays. Spontaneous activity was recorded daily during development; for each recording, up to 1,024 electrodes selected from 26,400 electrodes were monitored for 30 min. We applied principal component analysis (PCA) to binned population activity and quantified the rank-ordered variance spectrum by fitting a power law with an exponential cutoff. Across seven dishes, the PCA variance spectrum decayed exponentially in early developmental stages, but gradually transitioned to a power-law decay as cultures matured, stabilizing around day in vitro (DIV) 15 with a power-law exponent of approximately 1.2-1.3. Temporal shuffling, which disrupted inter-electrode correlations while preserving single-electrode activity statistics, abolished the power-law spectrum, indicating that coordinated temporal structure is critical for its emergence. We further found that the developmental emergence of the PCA power law coincided with neuronal avalanches: cascade-size distributions also transitioned from exponential to power-law decay around DIV 15, with an exponent close to 1.5. To examine a possible mechanism for this coexistence, we analyzed recurrent network models with different synaptic weight distributions. Networks with heavy-tailed connectivity reproduced the co-emergence of the PCA power law and neuronal avalanches, whereas Gaussian networks did not. These results show that scale-free high-dimensional population activity can self-organize in developing cortical networks without structured sensory inputs, and suggest that heavy-tailed connectivity may provide a common mechanism linking neural criticality and the geometry of population activity.

Disclosures: A. Nakamuta: None. **J. Teramae:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.20/MM10

Topic: J.06. Computation, Modeling, and Simulation

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 24K15104

Japan Agency for Medical Research and Development (AMED) AMED-CREST 26gm1510005s0206
JST BOOST, Grant Number JPMJBS2407

Title: Representational drift enables expansion of hippocampal cognitive maps to novel environments

Authors: *S. SHIGA, J.-N. TERAMAE;
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Abstract: The hippocampus is thought to support spatial navigation through the activity of place cells. These neurons are selectively activated when an animal occupies particular locations in an environment, known as place fields. By collectively covering the environment, place fields are believed to give rise to a population-level cognitive map that encodes spatial information. While individual place fields are stable over short timescales, recent advances in longitudinal recordings of large neuronal populations have revealed that place fields drift continuously over time, even while the ensemble representation stably covers the environment. Several theoretical studies have been proposed to explain the mechanisms underlying representational drift. However, in most of these works, drift has been treated as a byproduct of noisy neural or synaptic activity. Consequently, its functional role has remained largely unresolved. In this study, we develop a theoretical framework in which representational drift in hippocampal place cells plays an essential role in expanding the cognitive map from familiar to novel environments. Based on a recently proposed Bayesian framework that reproduces the stochastic properties of neurons and synapses, we provide a model of the hippocampal local circuit together with synaptic inputs from grid cells in the entorhinal cortex. We find that place fields and a stable cognitive map self-organize when the network is exposed to a novel environment. Owing to the intrinsic stochasticity of the model, individual place fields continue to drift even after learning, while the ensemble maintains stable coverage of the input space, reproducing experimentally reported features of representational drift. Significantly, we further find that representational drift allows the network to extend the cognitive map to newly encountered environments while preserving previously learned maps, enabling a balance between stability and plasticity. In contrast, if we artificially suppress the stochasticity of the model, the network fails to extend previously learned maps while maintaining their stability. Therefore, these findings provide theoretical evidence that representational drift is not merely noise but can serve as a mechanism supporting the adaptive expansion of spatial memory representations. More generally, they indicate that ongoing variability in neural circuits can play a constructive role in promoting generalization across environments.

Disclosures: S. Shiga: None. **J. Teramae:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.21/MM11

Topic: J.06. Computation, Modeling, and Simulation

Title: Predictive Mapping of Brain-Wide Bursting in Zebrafish

Authors: *W. QIN[1], H. NATSUKAWA[2], C.-M. YEH[3], S. CHALASANI[5], T. O. SHARPEE[4], G. M. PAO[6];
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Abstract: Spontaneous brain-wide bursts occurs when activities become synchronized across many neurons, yet the local neural dynamics that precede these events are not fully understood. Inspired by previous work showing that single neuron dynamics can contain early signatures of upcoming global bursts, we analyzed whole-brain calcium imaging data from zebrafish recorded under normoxia and hypoxia conditions. We used convergent cross mapping (CCM) to identify neurons whose activity could predict brain-wide burst events approximately half a second before burst onset. Notably, this predictive subset showed low correlation with the global activity signal, suggesting that these neurons do not simply mirror population-wide activity but may instead contain early information about transitions into a bursting state.
To examine how these predictive neurons are embedded within the broader network, we next applied CCM across all neuron pairs to estimate a brain-wide map of putative causal interactions. We then compared the causal inference patterns of the predictive subset with the anatomical locations of recorded cells to determine whether these neurons were spatially clustered, broadly distributed, or associated with specific brain regions. By combining nonlinear time-series prediction, causal mapping, and anatomical organization, this project investigates how local neural activity relates to spontaneous brain-wide bursting and how these relationships may change under hypoxic stress.

Disclosures: W. Qin: None. **H. Natsukawa:** None. **C. Yeh:** None. **S. Chalasani:** None. **T.O. Sharpee:** None. **G.M. Pao:** None.

Poster

PSTR250: Population Dynamics and Neural Representations

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR250.22/MM12

Topic: J.06. Computation, Modeling, and Simulation

Title: Low-Dimensional Brain-State Dynamics Across Electroconvulsive Therapy

Authors: *G. KANG[1], M. S. BREAULT[2], S. ORGUC[3], M. AREGAWI[4], B. TSENG[5], M. HENRY[6], R. J. HORVATH[7], S. SEINER[8], E. N. BROWN[9];
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[6]Massachusetts Gen. Hosp., Boston, MA; [7]Dept. of Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp. / Harvard Med. Sch., Lexington, MA; [8]McLean Hosp., Belmont, MA; [9]Brain and Cognitive Sci., MIT/Mass Gen. Hospital/Harvard Med. Sch., Cambridge, MA

Abstract: Electroconvulsive therapy (ECT) is among the most effective treatments for treatment-resistant depression, but its neurophysiological mechanisms remain poorly understood. Most EEG studies of ECT have focused on ictal activity and postictal suppression, but whether neural activity across the full procedure evolves as a continuous dynamical process remains unknown. We hypothesized that full-procedure ECT EEG can be represented as a low-dimensional dynamical process with structured, reproducible trajectories across treatment stages. To test this hypothesis, we analyzed EEG recordings from nine subjects spanning seven windows: baseline, anesthetic induction, pre-ictal, ictal, postictal, recovery, and emergence. Sliding windows were extracted throughout each session, and spectral features (delta, theta, alpha, beta, gamma, and total power) were computed for each window. Principal component analysis was used to construct a low-dimensional representation of EEG activity, which was then fit with a linear Gaussian state-space model to characterize latent-state evolution over time. Two latent dimensions accounted for approximately 95% of spectral variance. Across subjects, EEG activity evolved along a reproducible trajectory through latent space, with the first dimension reflecting coordinated changes in delta, theta, alpha, beta, and gamma power and the second capturing variation in spectral composition. Notably, the largest deviations from baseline and the fastest latent-state transitions occurred during the pre-ictal period, exceeding those observed during the ictal period itself. Gaussian mixture clustering identified distinct latent regions preferentially occupied during pre-ictal, postictal suppression, and recovery. The state-space model recovered a similar latent organization, supporting the robustness of the observed trajectory structure. These findings reveal that full-procedure ECT EEG evolves along a structured low-dimensional trajectory and that substantial neural reorganization precedes seizure induction. The prominence of pre-ictal dynamics suggests that neural state transitions preceding stimulation represent an underexplored component of ECT and warrant more rigorous investigation.

Disclosures: G. Kang: None. **M.S. Breault:** None. **S. Orguc:** None. **M. Aregawi:** None. **B. Tseng:** None. **M. Henry:** None. **R.J. Horvath:** None. **S. Seiner:** None. **E.N. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PASCALL.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.01/MM13

Topic: J.06. Computation, Modeling, and Simulation

Title: Identifying Static and Dynamic Single-Cell eQTLs across Human Prefrontal Cortical Layers

Authors: *Z. CHU[1], Y. SONG[1], M. GERSTEIN[2];
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Abstract: Genetic regulation in the human prefrontal cortex (PFC) is organized across discrete cell types and continuous neuronal and glial states, raising a fundamental question: at what cellular resolution should expression quantitative trait loci (eQTLs) be mapped? Pseudobulk analyses aggregate predefined populations but can lose power under sparse sampling and obscure effects that vary across cortical layers or cellular trajectories. We developed scPME-QTL, a single-cell Poisson mixed-effects framework that models raw unique molecular identifier counts with donor-level and technical covariates. By fitting one null model per gene and vectorizing score tests across cis variants, scPME-QTL achieved median per-gene runtimes of 24.4 seconds for its permutation-calibrated main mode and 3.5 seconds for its rapid mode, versus 35.2 minutes for full generalized linear mixed-model fitting. We applied scPME-QTL to >2.8 million nuclei from 388 adult human PFC samples across 18 excitatory, inhibitory, and non-neuronal populations. It recovered 85.6% of pseudobulk eGenes and identified 292 additional unique eGenes, a 20.3% increase, and was more robust to cell downsampling. Although most lead eQTLs were cell-type restricted, sharing reflected cortical organization: intratelencephalic neurons clustered across laminar subclasses, Pvalb and Sst interneurons shared regulatory effects consistent with developmental relatedness, macroglia clustered together, and microglia remained distinct. We next modeled genotype main effects as static eQTLs and genotype-by-state interactions as dynamic eQTLs along intratelencephalic laminar, Pvalb-Sst interneuron, and oligodendrocyte precursor cell-to-oligodendrocyte continua. Joint modeling increased sensitivity for static effects shared across adjacent cortical states. Dynamic regulation was limited along the Pvalb-Sst axis but implicated neuronal excitability, calcium transport, and synaptic modulation, whereas hundreds of dynamic eQTLs during oligodendroglial differentiation were enriched in synaptic transmission, glutamate receptor, calcium-signaling, and cell-interaction programs. These architectures establish scPME-QTL as a cell-typing diagnostic: extensive sharing, concordant effects, and limited dynamic regulation support joint mapping, whereas abundant genotype-by-state interactions indicate that related states require separation or explicit state-dependent modeling. Thus, matching cellular resolution to regulatory architecture reveals how genetic effects are shared or remodeled across the layered and continuous organization of the human PFC.

Disclosures: Z. Chu: None. **Y. Song:** None. **M. Gerstein:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.02/MM14

Topic: J.06. Computation, Modeling, and Simulation

Support: 32530027

Title: A high-resolution spatial computing framework resolving cortical laminar architecture and age-related circuit decline in the human cerebral cortex

Authors: *L. WANG[1], Y. WEI[2], Y. HE[2], Y. LIU[2];
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Abstract: Precise delineation of cortical layers is fundamental for understanding human brain organization and cell-type architecture. However, traditional anatomy-based methods often lack molecular resolution and suffer from significant inter-observer subjectivity. Furthermore, a high-resolution spatial blueprint capturing how these laminar microenvironments age across the human lifespan remains incomplete. To address this, we developed gene expression-defined cortical layers (GD-Ls), a high-resolution computational framework for cortical parcellation based on spatial transcriptomics (Stereo-seq). We first rigorously evaluated the algorithmic capabilities and generalizability of GD-Ls, demonstrating that the it accurately resolves fine-scale laminar boundaries and distinct sublayer domains within L1, L3, and L6, while exhibiting exceptional cross-platform and cross-species consistency. Crucially, we confirmed that GD-Ls possesses high translational sensitivity, successfully identifying localized laminar disorganization and aberrant neural-glial molecular signatures in pathologically altered tissues that are frequently obscured under conventional histology. Having established this robust and versatile framework, we scaled and applied it to a population-level atlas spanning 71 relatively healthy donors across the entire human lifespan, achieving single-cell resolution mapping of over 3.4 million segmented cortical cells across four lobes. Utilizing this standardized spatial baseline, we identified 906 layer-enriched expressions (GLEEs) showing highly conserved yet region-specific laminar patterns. Tracing these spatial coordinates across age groups unmasked a stereotyped, selective vulnerability of superficial cortical circuits during natural senescence. Notably, we captured an age-dependent proportional reduction of a specific somatostatin interneuron subtype (SST.17), which decoupled its localized interactions with L2/3 glutamatergic neurons through the programmed decay of SST-SSTR1 signaling. Together, our framework and lifespan baseline provide a standardized tool for human brain mapping, bridging verified computational parcellation with region-specific circuit aging to define the spatial niches driving early neuropathological transitions.

Disclosures: L. Wang: A. Employment/Salary (full or part-time):; BGI research. **Y. wei:** None. **Y. He:** None. **Y. liu:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.03/MM15

Topic: J.06. Computation, Modeling, and Simulation

Title: Tending a living atlas: capturing evidence for anatomical atlas changes

Authors: *A. A. BHANDIWAD[1], Q. WANG[3], S.-L. DING[4], D. FENG[1], T. S. MOLLENKOPF[2];
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Abstract: 3D brain atlases and Common Coordinate Frameworks (CCFs) are fundamental spatial references but also evolve over time based on integration of new datasets, including whole-brain spatial transcriptomics, histology, and connectivity data. The provenance and rationale for changes are distributed across multiple sources and disconnected from the atlas itself, creating a gap in users' understanding of what has changed over time and why. Here, we present a versioning schema for human, primate, and mouse CCF parcellations and terminology, together with an evidence graph model that links parcellation changes to the datasets and rationale that supports changes. As proof of principle, we apply this framework to recently parcellated basal ganglia subdivisions in the Allen Mouse Common Coordinate Framework version 3 (CCFv3). We show how the model enables users to query multimodal evidence that supports specific boundary refinements and to reconstruct the rationale for CCF parcellation updates. This approach makes 3D brain atlas evolution more transparent, reproducible, and accessible, improving the interpretation and reuse of CCF-dependent datasets.

Disclosures: A.A. Bhandiwad: None. **Q. Wang:** None. **S. Ding:** None. **D. Feng:** None. **T.S. Mollenkopf:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.04/MM16

Topic: J.06. Computation, Modeling, and Simulation

Support: NINDS U24NS146314

Title: Applying Universal Cell Embedding foundation model to integrate and map brain single-cell transcriptomics data

Authors: B. CRAFT[1], K. PANG[2], **M. GOLDMAN**[1], Y. ROSEN[3], J. ZHU[1], *D. HAUSSLER[1];
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Abstract: The rapid expansion of single-cell transcriptomic data in neuroscience has outpaced existing integration tools, which remain semi-automated and limited to a few million cells. We present a framework for building comprehensive brain single-cell transcriptome references by applying the Universal Cell Embedding (UCE) foundation model, a 650-million-parameter transformer trained on 36 million cells across 300+ datasets and 8 species, to integrate data from major neuroscience consortia including BICAN and SEA-AD. Our reference encompasses 20 million human nervous system cells from 92 studies, spanning diverse brain regions,

developmental stages, and disease states. We demonstrate that UCE inference enables robust mapping of new datasets onto the reference, achieving high ontology-aware prediction accuracy across varied cell types and preprocessing pipelines. It outperforms existing tools such as SCimilarity and is on par with MapMyCells in cross-ontology benchmarks.
To support broad community use of these references, we are developing the UCSC Brain Explorer, a web portal that enables researchers to map their own single-cell data to the references and explore the results interactively. It leverages pyramid data tiling to visualize tens of millions of cells in under 0.5 seconds with interactive panning and zooming. The website currently supports three references: adult human brain, developing human brain, and human brain organoid. Researchers upload their h5ad file, which is then embedded using UCE, projected into a reference, and assigned cell labels based on the 30 nearest reference neighbors. Users can interactively explore the mapping overlaid on top of the reference UMAPs, download the cell labeling results, and explore additional analyses, such as differential gene expression, using our chatbot. The UCSC Brain Explorer is currently in beta and open for public use and feedback.

Disclosures: B. Craft: None. **K. Pang:** None. **M. Goldman:** None. **Y. Rosen:** None. **J. Zhu:** None. **D. Haussler:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.05/MM17

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant UM1MH130981
NIH Grant DP2MH140136
Klingenstein–Simons Fellowship (F.M.K.)
NIH Grant 5T32MH065214

Title: PIANO: Atlas-Scale Integration and Generative Modeling of Single-Cell Multiomics for Cross-Species and Drug Perturbation Analyses

Authors: *N. WANG[1,2], C. CARDENAS[1], V. E. NIETO CABALLERO[1], D. M. TURNER[1], H. FEINBERG[1], D. YUAN[2], N. SCOTT[1], M. DEBERARDINE[1], S. DAN[1], L. CACERES[1], J. SCHEMBRI[1], Z. YAO[2], C. LEE[2], J. W. PILLOW[1], F. M. KRIENEN[1];
[1]Princeton Univ., Princeton, NJ; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Single-cell sequencing enables high-throughput transcriptomic profiling, supporting the creation of comprehensive brain cell type atlases comprising millions of individual cells and nuclei. These datasets span multiple donors and species, creating rich opportunities for evolutionary comparisons of cell type diversity across mammalian brains. However, single-cell data are sparse, noisy, and affected by batch effects arising from differences in donors and sequencing platforms, which complicate biological comparisons across conditions.

To address these challenges, data integration is a crucial step in most single-cell analyses. A common approach is to use machine learning models such as variational autoencoders (VAEs) to learn a shared latent representation. Through non-linear dimensionality reduction, VAEs learn an informative latent space that mitigates sparsity and noise while incorporating batch covariates to reduce unwanted variation. However, existing approaches treat covariates primarily as nuisance factors to be removed, underutilizing the generative capabilities of VAEs to model how biological variables influence gene expression.
We developed PIANO (Probabilistic Inference Autoencoder Networks for multi-Omics), a fast, robust, and scalable deep learning framework for integration and generative modeling of single-cell multiomics data. PIANO outperforms existing approaches by achieving stronger batch correction while preserving higher-resolution biological structure in the latent space. Additionally, PIANO explicitly models how biological covariates influence gene expression, empowering downstream analyses.
Applied to a primate basal ganglia atlas, PIANO reveals cell-type-specific differential gene expression across species while disentangling these differences from confounding global species effects. Moreover, PIANO's speed and scalability enable the analysis of an entire drug perturbation atlas containing over 100 million cells—without subsampling due to runtime or memory constraints—recovering disease-relevant drug-induced responses in established signaling pathways that are otherwise obscured by the inherent sparsity and noise of single-cell transcriptomics data.
These results establish PIANO as a versatile framework for atlas-scale data integration and generative modeling, enabling biological discovery across evolutionary, disease, and perturbation contexts.

Disclosures: N. Wang: None. **C. Cardenas:** None. **V.E. Nieto Caballero:** None. **D.M. Turner:** None. **H. Feinberg:** None. **D. Yuan:** None. **N. Scott:** None. **M. DeBerardine:** None. **S. Dan:** None. **L. Caceres:** None. **J. Schembri:** None. **Z. Yao:** None. **C. Lee:** None. **J.W. Pillow:** None. **F.M. Krienen:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.06/MM18

Topic: J.06. Computation, Modeling, and Simulation

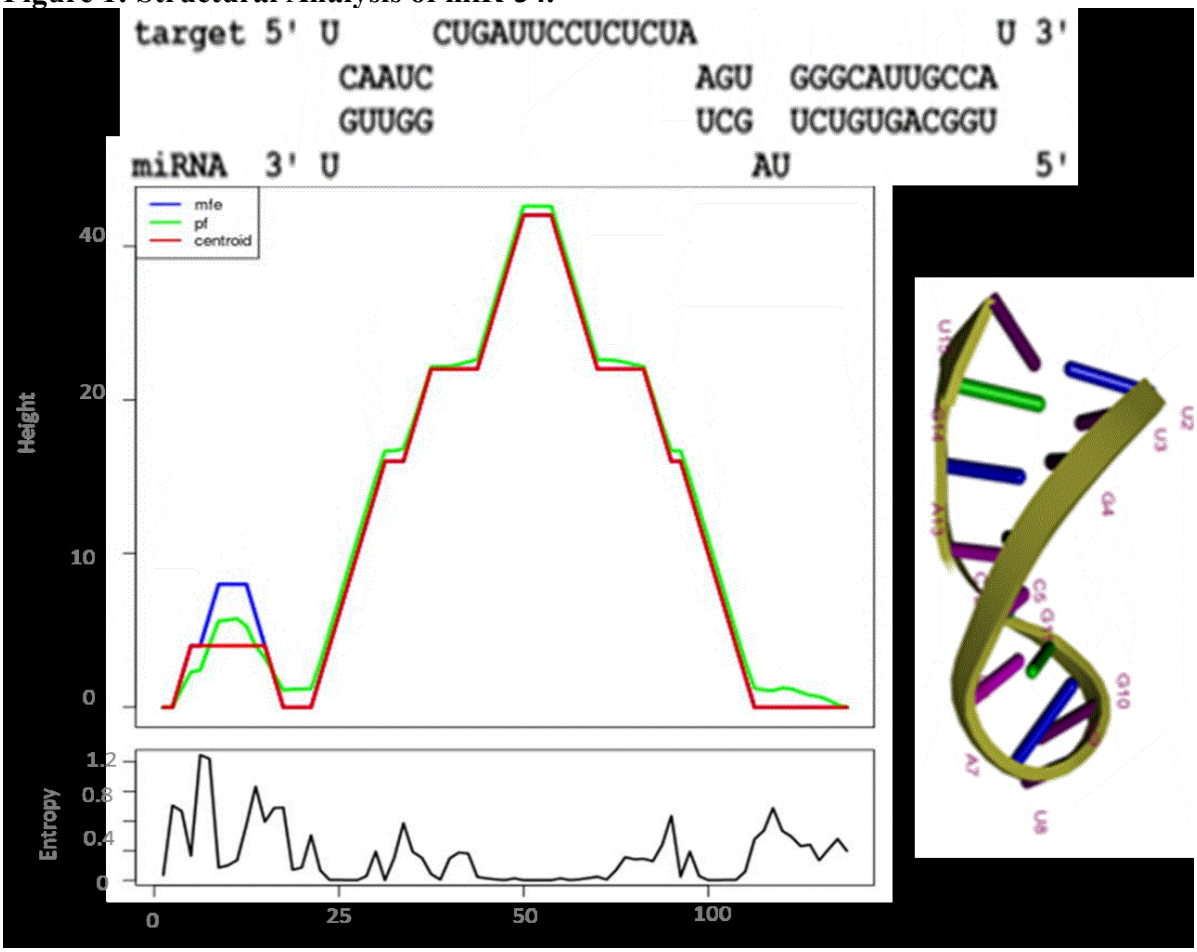
Title: Structural analysis of the noncoding RNA in Parkinsons disease: Towards targeting specificity and biomarker discovery

Authors: *P. K. AVTI, S. KUMAR;
Biophysics, Post Grad. Inst. of Med. Educ. and Res. (PGIMER), Chandigarh, India

Abstract: Structural Analysis of the non-coding RNAs in Parkinson’s disease: Towards targeting specificity and biomarker discovery**Pramod K Avti*,** Sachin Kumar**Department of**

Biophysics, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India – 160012Email: pramod.avti@gmail.com The structural elucidation of the distinct and intricate roles of microRNAs (miRNAs) in the pathophysiology of Parkinson's disease (PD) is emerging as a vital platform for biomarker discovery and therapeutics. Therefore, identification of highly regulated miRNAs sheds light on their pivotal roles through structural modeling. To achieve this goal, computational tools such as RNAfold, miRBase, 3DRNA, and miRnet were used to elucidate precursor and mature miRNA's 2D and 3D structural information. Highly regulated miRNAs and their target genes were identified in PD. These genes span various classes, including lipid signaling pathways, inflammatory pathways, mTOR pathways, MAP kinases, Transcription factors, and matrix metalloproteinases. Further, specific and unique molecular hybridization features [such as seed sequence complementarity, canonical base pairing, absence of G-U pairs, and minimum free energy] within the miR-mRNA hybrid complex determine the structural features and functional aspects of these molecules. These structural elucidations not only provide the thermodynamically stable insights but also the regulatory gene interactions at the cellular level that help develop small therapeutic molecules. Understanding the structural intricacies of highly regulated miRNAs unveils their pivotal roles in influencing crucial pathways implicated in Parkinson's disease. **Keywords:** Canonical base pairing, Minimum Free Energy, Non-coding RNAs, Parkinson's disease, **Conflict of Interest**: All the authors declare no conflict of interest**Ethical Consideration**: As this is a computational study, no ethical approval is required**Funding**: None

Figure 1: Structural Analysis of miR-34.



ReferencesNucleic Acids Res (2019) 47:D155-D162
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Int J Mol Sci. (2019) 20(17):4116.
RNA, 2004. doi:10.1261/rna.5248604RNA 2004. 10: 1507-1517

Disclosures: P.K. Avti: None. **S. Kumar:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.07/MM19

Topic: J.06. Computation, Modeling, and Simulation

Support: U01 ES-035843
ZIA-ES103404

Title: Complementary Analytical Approaches Reveal Expanded Transcriptomic Signatures in the Ventral Hippocampus Following Developmental Flame Retardant Exposure

Authors: *J. BERGER[1], A. J. NEWELL[1], A. M. BROOKS[1], S. GILLERA[2], L. LIU[1], K. E. GERRISH[1], H. B. PATISAUL[1];
[1]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]North Carolina State Univ., Raleigh, NC

Abstract: Transcriptomic studies generate high dimensional datasets containing thousands more attributes than replicates, creating challenges for standard statistical approaches. Traditional differential expression analysis uses linear statistics and strict statistical correction for multiple comparisons to avoid false positives. However, this stringency can obscure small consistent changes in networks of related genes, particularly in brain, where small fold changes can have functional impact. Machine learning algorithms provide an orthogonal approach that complements these methods by identifying gene sets that optimize classifier performance. Together, these approaches capture shared and unique transcriptomic variation, expanding molecular signatures and biological insight beyond either approach alone. To evaluate this framework, we analyzed ventral hippocampal RNA-seq data from prairie voles developmentally exposed to the commercial flame retardant mixture FireMaster 550 (FM550). Early-life exposure has been linked to social and cognitive impairments in humans; therefore, exposure was restricted to either gestation or lactation (1000 µg/day FM550 or vehicle control via oral dosing to the dam). In adulthood, ventral hippocampal tissue was collected from offspring and transcriptomic profiles were assessed using differential expression analysis and machine learning feature selection. These approaches identified overlapping and distinct gene patterns, with ventral hippocampal gene expression strongly shaped by exposure timing, sex, and their interaction, expanding candidate genes beyond those identified through differential expression

alone. Pathway analyses of these gene sets revealed enrichment of processes related to neuronal development and synaptic transmission. These findings demonstrate the value of combining machine learning with conventional RNA-seq workflows to identify high information molecular signatures, prioritize candidate genes for follow up investigation, and enhance discovery of neurobiologically relevant pathways in high dimensional datasets. Importantly, this combinatorial approach provides a generalizable strategy that can be incorporated into diverse workflows to prioritize biologically meaningful information early and support biomarker discovery.

Disclosures: J. Berger: None. **A.J. Newell:** None. **A.M. Brooks:** None. **S. Gillera:** None. **L. Liu:** None. **K.E. Gerrish:** None. **H.B. Patisaul:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.08/MM20

Topic: J.06. Computation, Modeling, and Simulation

Title: Buildout of a library to analyze, visualize, and interface with multiple brain atlases

Authors: *R. BOSE-ROY;
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Abstract: Brain atlases are central to modern neuroscience, providing standardized representations of anatomical and functional organization across imaging modalities. However, existing analysis pipelines can be atlas-specific, modality-specific, or have difficulty integrating neuroimaging, electrophysiology, connectivity, and spatial information. This work demonstrates the buildout of a computational framework for the analysis and visualization of brain atlases as programmable, extensible data structures capable of supporting multimodal analyses across scales. The framework represents individual brain parcels as independent objects while maintaining synchronization with a global atlas representation. Atlas features, including parcel geometry, connectivity matrices, and user-defined data types, can be created, accessed, and modified at either the parcel level or whole-brain level. Changes propagate automatically between representations, enabling flexible manipulation of regional and network-level information while preserving consistency throughout the atlas. The framework further supports spatial querying, neighborhood searches, hierarchical attribute management, and integration of high-dimensional data structures including tensors, matrices, graphs, and time-varying signals.This work demonstrates use of this computational framework across multiple high-resolution atlases, as well as to arbitrary user-defined parcellations. This design enables standardized analyses across atlases while reducing the need for custom code development for individual datasets. By unifying anatomical representations, network models, and multimodal neuroscience data within a single computational architecture, this framework provides a scalable

foundation for brain network analysis, connectomics, electrophysiology, and neuroimaging applications.

Disclosures: R. Bose-Roy: None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.09/MM21

Topic: J.06. Computation, Modeling, and Simulation

Title: GAUGE: Geometry-aware unified grid embedding for standardized cross-sample spatial transcriptomics comparison

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Univ. of Chinese Acad. of Sci., Hangzhou, China

Abstract: Spatial transcriptomics has generated vast datasets across species, developmental stages, and pathological conditions, yet systematic cross-sample comparison remains challenging due to geometric complexity and morphological variability of tissues. Existing spatial alignment approaches rely on expression similarity or simplified geometric assumptions, limiting their applicability to morphologically complex domains. Here we present GAUGE, a framework that constructs intrinsic canonical coordinate systems on arbitrarily shaped tissue regions. By defining anatomical anchor points and leveraging physics-inspired geometric computations, GAUGE transforms complex tissues into standardized matrices directly comparable across samples, handling diverse geometries from highly folded cortical structures to curved embryonic tissues. We validated GAUGE across over 100 spatial transcriptomics samples spanning multiple species, including developmental brain atlases, mouse organogenesis, human intestinal and skin tissues, and neurodegenerative disease. Coordinate-aware decomposition on the standardized grids identified spatially graded gene modules and cell-type distribution patterns, revealing conserved spatial transcriptional programs across species and developmental stages. GAUGE provides a general, platform-agnostic framework enabling systematic spatial transcriptomics comparison.

Disclosures: T. Feng: None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.10/MM22

Topic: J.06. Computation, Modeling, and Simulation

Support: P51-OD011132 (NIH support to ENPRC)
R01NS130551 (NIH/NINDS)
1R21NS123487 (NIH/NINDS)
1P50NS123103-01 (NIH/NINDS)

Title: Systematic Analysis of AAV-Mediated Transgene Expression in the Macaque Brain

Authors: *Z. HERRERA[1], E. M. BOSSARD[1], R. S. YENDAMURI[1], A. GALVAN[2];
[1]Emory Natl. Primate Res. Ctr., [2]Emory Natl. Primate Res. Center, Dept. of Neurology, Sch. of M, Emory Univ., Atlanta, GA

Abstract: Adeno-associated viral vectors (AAVs) are extensively used in neuroscience to transduce brain cells with neuromodulators and sensors, including opsins, chemogenetic receptors, calcium sensors, and tracing proteins. In non-human primates, AAVs are particularly valuable because transgenic approaches are not feasible. Despite its extensive use, few studies have systematically examined how factors such as AAV serotype, injection volume, target location, and promoter-enhancer sequences influence transgene expression in the primate brain. These variables are likely to affect the spread of a viral construct and transgene expression. Understanding these factors may help to optimize AAV-mediated protein expression. To address this gap, we developed an automated deep-learning pipeline to quantify post-mortem transgene expression visualized by immunoperoxidase labeling against the AAV-encoded tag protein in the macaque brain. The pipeline objectively estimates AAV spread by: (1) classifying pixels into cell bodies and neuropil using a UNet++ model with an EfficientNet-B0 encoder trained on digitized whole-slide brain sections; (2) outlining the transfected injection site using density-based clustering (DBSCAN); and (3) estimating injection site volume by integrating transfected area across sections using area under the curve (AUC).Initial analyses of bi-hemispheric AAVdj-PSAM-GlyR4-HA injections in the internal globus pallidus (monkeys G and W; 20 and 14µl/hemisphere respectively) and subthalamic nucleus (monkey Z; 19 and 20µl/hemisphere) showed reproducible viral spread across hemispheres. Estimated AUC volumes were comparable within animals, with mean RH-LH differences of 8.9% across monkeys W (142.6 mm^3 LH; 143.9 mm^3 RH), G (161 mm^3 LH; 138mm^3 RH), and Z (94 mm^3 LH; 103.8 mm^3 RH).These results indicate that our workflow efficiently and objectively estimates transgene expression volume. We will extend this analysis to a large dataset of more than 300 intracerebral AAV injections performed in macaques by our laboratory, including additional serotypes, injection volumes, and brain regions. Together, these findings may guide future intracerebral AAV injections in macaques and provide a broadly applicable method for quantifying immunohistochemistry-positive elements.

Disclosures: Z. Herrera: None. **E.M. Bossard:** None. **R.S. Yendamuri:** None. **A. Galvan:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.11/MM23

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant U24NS135547
NIH OT2OD030541

Title: Enhancing SPARC Connectivity Knowledgebase with Molecular and Functional Profiles: Bridging Connectivity to Candidate PRECISION Cell Types

Authors: F. T. IMAM[1], T. GILLESPIE[1], I. ZIOGAS[2], S. TAPPAN[3], J. BOLINE[4], *J. S. GRETHE[1], M. E. MARTONE[1];
[1]Neurosciences, Univ. of California San Diego, La Jolla, CA; [2]SPARC K-Core, La Jolla, CA; [3]Rock Maple Sci., Hinesburg, VT; [4]Informed Minds Inc, Walnut Creek, CA

Abstract: The SPARC Connectivity Knowledgebase (SCKAN) is a highly curated resource encoding evidence-based neural connectivity at the neuron population level using the Neuron Phenotype Ontology (NPO). Each population represents a theoretical grouping of neurons based on shared phenotypic properties, rather than specific cell type. SCKAN populations are characterized by anatomical trajectory (soma, axon terminals, and axonal route) of neural pathways. Currently, SCKAN comprises 502 populations spanning the ANS, major sensory and motor pathways, and generic nociceptive circuits. SCKAN is accessible through SPARC's interactive connectivity maps, SCKAN Explorer, and an AI-powered natural language interface. While SCKAN captures anatomical connectivity, it does not link its populations to defined cell types such as those identified by the NIH PRECISION Human Pain Network. Part of HEAL, PRECISION is performing comprehensive molecular phenotyping of human cells involved in chronic pain, including single cell phenotyping of dorsal root ganglion (DRG) and the trigeminal ganglion (TG). Using NPO, we modeled DRG and TG cell types based on six major sc/snRNA-seq publications. This enabled classification of these cell types across sources, spanning low-threshold mechanoreceptors, peptidergic and non-peptidergic nociceptors, proprioceptors, and thermoreceptors. These cell types carry rich phenotypic profiles such as marker genes, fiber types, and functional modality, but lack explicit links to SCKAN's anatomical connectivity records. We present a strategy for bridging SCKAN populations to candidate PRECISION cell types using NPO as the shared backbone. The approach uses organ-level tracing studies to infer candidate cell types from molecular markers of organ-innervating populations in SCKAN. For example, authoritative sources used to model the renal DRG afferents in SCKAN cite CGRP+/Substance P+ fibers (mouse) and PIEZO2+ fibers (human), suggesting assignments to peptidergic C-fiber and Aβ/Aδ fibers respectively. These constraints narrow compatible PRECISION subtypes by filtering candidates by species, fiber type, and marker genes, yielding NPO-defined classes such as DRG C-PEP subtypes for CGRP+ C-fibers, linked to SCKAN populations as provisional candidates. Two enrichment steps enable this: adding fiber type phenotypes (Aβ/Aδ/C) to SCKAN's DRG populations lacking them and adding projection phenotypes to align with cell type representations. The result is a candidate-level linkage connecting SCKAN connectivity to molecularly defined cell types, datasets, connectivity maps, and cellular phenotypes within the SPARC Knowledge Graph.

Disclosures: F.T. Imam: None. **T. Gillespie:** None. **I. Ziogas:** None. **S. Tappan:** None. **J. Boline:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.12/MM24

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R24MH114785
Johns Hopkins Applied Physics Laboratory internal research and development funds

Title: Confound: a dense neural segmentation model for large-scale connectomics

Authors: *H. MARTINEZ, J. MATELSKY, L. KITCHELL, D. XENES, G. W. MILSAP, E. C. JOHNSON, B. A. WESTER;
Johns Hopkins Applied Physics Lab., Laurel, MD

Abstract: Advances in nanoscale neuroanatomy and connectomic analysis increasingly depend on scalable, generalizable neuron segmentation that can operate across diverse species, anatomical regions, and high-resolution imaging modalities. We present a large-scale cell segmentation foundation model that explicitly learns dataset-level representations to improve segmentation performance and generalizability across different volumetric collections of electron microscopy (EM) data. We first aggregated publicly available high-resolution imaging datasets coupled with registered segmentation that spanned multiple species, brain regions, resolutions, and imaging modalities. We then trained a bespoke, metadata-aware Swin U-net architecture that incorporates contextual information including imaging resolution, anatomical region, species, and acquisition modality (e.g., SEM, TEM, LICONN) via a side-channel autoencoder. In addition to evaluating segmentation quality against a held-out series of datasets, we also performed inference on a novel, held-out mammalian optic nerve dataset. Our model achieves state of the art performance without the need for extensive retraining on the underlying image data. We also share a reconstruction pipeline that exports supervoxelized results directly to the BossDB data archive and the Connectomics Annotation Versioning Engine (CAVE) for subsequent agglomeration, proofreading, and analysis. This capability enables a complete data-generation workflow while maintaining compatibility with existing community connectomics infrastructure. Together, these results demonstrate the feasibility of a foundation model for neuron reconstruction built with community-supported tools and establish a scalable pathway toward next-generation connectomics workflows.

Disclosures: H. Martinez: None. **J. Matelsky:** None. **L. Kitchell:** None. **D. Xenes:** None. **G.W. Milsap:** None. **E.C. Johnson:** None. **B.A. Wester:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.13/MM25

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH R01AG065206
The Sapp Family Foundation
The Newman Research Fund
Knight Initiative for Brain Resilience at Stanford (CJS)
HHMI Hanna Gray Fellowship (MSM)

Title: A Computational Pipeline For Analyzing In-Situ Hybridization Images to Detect Cell-Type Specific Changes In Alzheimer's Model Mice

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disease that manifests in the aging adult brain. Yet growing transcriptomic evidence suggests that neuron-intrinsic molecular disruptions emerge far earlier, before cognitive decline and before conventional tools can reliably detect them. Understanding these earliest changes requires cell-type resolution that bulk sequencing cannot provide, such as RNA scope in situ hybridization. Existing analysis tools for single-cell mRNA quantification are often inaccessible or inflexible. We developed a trainable, open-source pipeline to detect and quantify neuronal changes. We hypothesized that synaptic changes in APP/PS1 mice at postnatal day 30 (P30) are accompanied by cell-type-specific transcriptional alterations, detectable prior to overt neuropathology. To test this, RNAscope fluorescence in situ hybridization was performed on layer 2/3 visual cortex brain sections from APP/PS1 and wild-type Ribotag mice (n=3-4 per genotype). Five candidate genes identified in neuronal Ribotag experiments were significantly upregulated at P30 in APP/PS1 mice. Their expression was quantified using ImageJ's open-access WEKA machine learning classifier trained on a three-class scheme (puncta, background, & cellular noise). A custom MATLAB application performed batch colocalization with VGLUT-positive excitatory and GAD-positive inhibitory neuron masks. Validation against ground truth annotations revealed no significant difference in puncta counts (paired t-test, $p>0.05$), with classifier precision of 0.95 and recall of 0.84. Critically, the pipeline processes a full batch (6-10 images) with colocalization metrics in minutes, compared to the hours of manual annotation completed for validation. Using our custom computational method, we discovered cell-type-specific dysregulation in APP/PS1 mice. Inhba was bidirectionally regulated, elevated in excitatory but decreased in inhibitory neurons. Penk and Pde10a were selectively upregulated in excitatory neurons; Acvr1c was exclusively

upregulated in inhibitory neurons. These findings reveal cell-type-specific transcriptional disruption preceding AD pathology and establish a validated open-source tool for single-cell mRNA quantification in various disease models.

Disclosures: N. Shree: None. **M.S. Mendes:** None. **J. Tomorsky:** None. **J. Huang:** None. **C.J. Shatz:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.14/MM26

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH Grant R01NS39600
NIH Grant R21AG87912

Title: Databases for neural morphology and hippocampal cell types

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Abstract: The tree-like morphology of neurons and glia is a key cellular determinant of circuit connectivity and metabolic function in the nervous system of essentially all animals. To elucidate the contribution of specific cell types to both physiological and pathological brain states, it is important to maximize accessibility to detailed and well documented neuroscience data. Here we discuss two mature neuroinformatics projects aimed at facilitating computational modeling and quantitative analysis of neural morphological and network dynamics. NeuroMorpho.Org is the largest online collection of freely available digital neural reconstructions, with hundreds of thousands of reconstructed morphologies and related metadata, and is continuously updated with new datasets. Our semi-automated pipeline enables the release of new data as soon as they are ready, maximizing the collective benefit of research and forging a positive culture of open data. On the other hand, Hippocampome.org uses axonal and dendritic morphology as a foundational approach to classify neurons in the rodent hippocampal formation. This curated knowledge base defines over 180 neuron types across the dentate gyrus, CA3, CA2, CA1, subiculum, and entorhinal cortex. Hippocampome.org then organizes known characteristics of neuron types by linking neuronal morphology to transcriptomics, electrophysiology, cell counts, synaptic signaling, connection probabilities, and more. All properties are directly supported by peer-reviewed experimental evidence and best fitted with computational models. Thus, Hippocampome.org enables building real-scale, biologically detailed, data-driven spiking neural network simulations. Both NeuroMorpho.Org and Hippocampome.org are fully open source, extensively documented, and programmatically accessible, enhancing the usability of existing data for rigorous analysis and realistic models from single cell to neural circuits and beyond.

Disclosures: C. Tecuatl: None. **G.A. Ascoli:** None.

Poster

PSTR251: Cells to Circuits at Scale: Omics, Connectomics, and Brain Atlases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR251.15/MM27

Topic: J.06. Computation, Modeling, and Simulation

Support: National Research Foundation of Korea (NRF) RS-2026-25475246
National Research Foundation of Korea (NRF) RS-2023-00209473
National Research Foundation of Korea (NRF) RS-2023-00264409
Korea Basic Science Institute (National Research Facilities and Equipment Center) grant funded by the Ministry of Science and ICT RS-2024-00401676
Bio & Medical Technology Development Program through the NRF funded by the Ministry of Science and ICT RS-2021-NR056586
BK21 plus program through the NRF funded by the Ministry of Education of Korea
Research Grant from HFSP (RGP003/2024)
KAIST Quantum+X Convergence R&D Project
KAIST C2(Creative & Challenging) Project

Title: Automated analysis of densely labeled expansion microscopy images using electron microscopy resources

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Abstract: Understanding cellular mechanisms requires nanoscale imaging approaches that capture both molecular specificity and ultrastructural context. Expansion microscopy with antibody and pan-protein staining offers a promising alternative to electron microscopy by enabling densely labeled volumetric imaging with optical microscopy. However, these images often lack the sharp contrast and structural clarity associated with electron microscopy, making interpretation more challenging and limiting their compatibility with existing computational tools developed for electron microscopy data. Here, we introduce a self-supervised deep learning framework that transforms expansion microscopy images into virtual electron microscopy-like images with enhanced contrast and more clearly defined structural boundaries. By leveraging information learned from electron microscopy data, this approach helps bridge the gap between optical and electron microscopy modalities while reducing the need for manual annotation or model retraining. Overall, this framework provides a path toward automated, high-throughput analysis of densely labeled expansion microscopy volumes, with potential applications across neuroscience, cell biology, and cancer research.

Disclosures: J.Y. You: None. **M. Eom:** None. **Y. Yoon:** None.