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Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.01

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

Support: NIA supplements to UG3DA047713

Title: Links between Alzheimer's disease neurofibrillary pathology and PTPRD regulation of neuronal GSK3 tau kinase activities support novel therapeutic candidate 6BrQGs

Authors: *G. R. UHL[1], J. CHOI[2];
[1]Univ. of Maryland Sch. of Med. and VA Maryland, Baltimore, MD; [2]Res., VA Maryland, Baltimore, MD

Abstract: Evidence from a variety of sources now links activities of the receptor type protein phosphatase D (PTPRD) to neuronal activities of the glycogen synthase kinases 3s and to Alzheimer's disease (AD) tau pathology. Human and mouse genetic differences that reduce levels of PTPRD expression accelerate accumulation of neuronal hyperphosphorylated tau neurofibrillary pathology. Flavonol positive allosteric modulation (PAM) of PTPRD actions in dephosphorylating and downregulating GSK3s provides a basis for links between flavonol intake and levels of AD or AD neurofibrillary pathology in genetically vulnerable mice and humans. We have identified an improved flavonol analog PTPRD PAM prodrug, 6BrQG and its active metabolite, 6BrQ based on screens of > 100 analogs for activities in enhancing PTPRD's dephosphorylation of phosphorylated (pY)GSK3s. 3xTg-AD/PTPRD+/- mice develop AT-8 immunoreactive hyperphosphorylated tau in many hippocampal neurons by 4 months of age, allowing tests of PTPRD inhibitors and PAMs. Treatment of 3xTg-AD/PTPRD +/- mice from weeks 6- 16 with alternating day quercetin reduces this accumulation by about half. Week 6-16 treatment with our improved PTPRD PAM active metabolite, 6BrQ, virtually eliminates this accumulation. While there is virtually no hippocampal AT-8 immunoreactivity in 4 month old 3xTg-AD mice, week 6-16 treatment with our irreversible PTPRD phosphatase inhibitor pentilludin results in many AT-8 positive hippocampal neurons. Identifying shorter pharmacologic treatments that might alter pathology wouldl aid translation of these results to humans. Treatment of 3xTg-AD mice with pentilludin from weeks 14-16 leads to almost 60% as many AT-8 immunoreactive hippocampal neurons as treatment from weeks 10-16 (75 *vs* 126 neurons/half brain section). The first 3xTg-AD/ PTPRD+/- mice treated for 4 weeks with 6BrQ display half as many AT-8 neurons as mice treated for 10 weeks with quercetin. Pharmacologic changes in PTPRD activities for more modest fractions of the mouse lifespan can thus dramatically influence development of neuronal neurofibrillary pathology in those with vulnerable genetic backgrounds. Taken together, this work continues to encourage advancing PTPRD PAMs for prevention and, possibly, treatment of neurofibrillary pathology in AD, and perhaps other tauopathies.

Disclosures: G.R. Uhl: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Coinventor on VA intellectual property for 6BrQG. **J. Choi:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.02

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

Support: Freedom Together Foundation
NINDS Grant 5R21AG088501
Ting Tsung and Wei Fong Chao Foundation
Howard Hughes Medical Institute
Jan and Dan Duncan Neurological Research Institute (NRI) at Texas Children's Hospital and the BCM-IDDRC (P50HD103555)

Title: LMO7 suppresses CHIP-dependent tau clearance via BAG5 and provides a therapeutic target in tauopathies

Authors: *J. KIM[1], B. TADROS[2], Y. WEI[3], S. JUNG[4], X. DENG[6], J. XU[5], H. Y. ZOGHBI[7]; [2]Neurol., [3]Mol. and Human Genet., [4]Biochem. and Mol. Pharmacol., [5]Departments of Neuroscience, Pediatrics, and Neurol., [1]BCM, Houston, TX; [6]Human and molecular genetics, Baylor Col. of Med., Houston, TX; [7]Mol. and Human Genet., Baylor Col. of Medicine/HHMI, Houston, TX

Abstract: Tauopathies, including Alzheimer's disease, lack disease-modifying therapies that effectively lower tau through small molecule enhancement of its clearance. Using cross-species genetic screens in human cells and *Drosophila*, we previously identified multiple regulators of tau levels. Among these, three independently selected hits—USP7, RNF130, and RNF149—converge on a common pathway centered on the E3 ubiquitin ligase Carboxy-Terminus of Hsp70-Interacting Protein (CHIP), highlighting a central for CHIP in maintaining tau homeostasis.Beyond this regulatory axis, we identified LIM domain only protein 7 (LMO7) as a previously unrecognized regulator of tau in both human cells and mouse brain. Adult knockdown of LMO7 reduced total and pathologically phosphorylated tau, attenuated gliosis, and rescued memory deficits in a tauopathy mouse model, supporting LMO7 as a promising therapeutic target for tauopathies.Mechanistically, we found that LMO7 mediates the interaction between CHIP and its inhibitor BAG5, thereby suppressing CHIP E3 ligase activity and limiting tau ubiquitination and degradation. As proof of concept, a CHIP-derived competing peptide targeting the LMO7-binding region simultaneously disrupted the LMO7-CHIP and CHIP-BAG5 interactions, resulting in CHIP activation and reduced tau accumulation. Together these findings identify the CHIP-LMO7-BAG5 complex as a druggable regulatory node controlling tau

proteostasis and reveal a therapeutically actionable mechanism for enhancing CHIP-dependent protein quality control, with implications for Alzheimer's disease and STUB1-associated ataxias.

Disclosures: J. Kim: None. **B. Tadros:** None. **Y. Wei:** None. **S. Jung:** None. **X. Deng:** None. **J. Xu:** None. **H.Y. Zoghbi:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.03

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

Support: Start-up fund from the Department of Biology at Syracuse University

Title: Inhibition of tau aggregation by a BBB-penetrating peptide to mitigate neurotoxicity in cellular and mouse model of tauopathies

Authors: *M. HASAN[1,2], A. FRANCO[3], K. ABD-ELRAOUF[1,2], D. MURPHY[1,2], J. ZENG[3,2], C. LO[1,2];
[1]Dept. of Biol., [2]Interdisciplinary Neurosci. Program, [3]Dept. of Chem. and Biomed. Engin., Syracuse Univ., Syracuse, NY

Abstract: Inhibition of tau aggregation by a BBB-penetrating peptide to mitigate neurotoxicity in cellular and mouse models of tauopathies
Mahmudul Hasan[1,2], Antonio Javier Franco Aguado[3], Kholoud Abd-ElRaouf[1,2], Dylan Murphy[1,2], Jialiu Zeng[2,3], Chih Hung Lo[1,2,*]
[1]Department of Biology, Syracuse University, NY 13244, USA[2]Interdisciplinary Neuroscience Program, Syracuse University, NY 13244, USA[3]Department of Chemical and Biomedical Engineering, Syracuse University, NY 13244, USA
Abstract Alzheimer's disease (AD) and tauopathies are neurodegenerative diseases with a histopathological hallmark of tau paired helical filament (PHF) and neurofibrillary tangle formation and are currently lacking effective treatment. Although several tau-targeted small molecules have advanced to clinical development, the potential of therapeutic peptides has not been comprehensively investigated. In this study, we conducted virtual screening using a cryo-EM structure of AD-derived PHF and a database of blood-brain barrier (BBB)-penetrating peptides and identified top 10 peptides for subsequent molecular dynamics simulation analysis and experimental validation. Tau aggregation kinetics were assessed using the thioflavin-T assay to examine aggregation behavior and neuroprotective properties. The peptide PP was identified as a promising candidate for inhibiting tau aggregation. Using fluorescence resonance energy transfer (FRET)-based tau biosensor expressed in HEK293 cells and imaging analysis, we found that PP effectively reduced FRET signal and inhibited tau puncta formation. In addition, PP rescued neuronal cell death in tauP301L-expressing SH-SY5Y cells. Our preliminary data further show that PP reduces tau pathology and restores cognitive function in tauP301S (PS19) mice.

Future research will employ biomolecular interaction analysis and nuclear magnetic resonance spectroscopy to understand the mechanistic basis and binding kinetics of PP in inhibiting tau aggregation. Collectively, our study identifies PP as a BBB-penetrating peptide that can effectively inhibit tau aggregation and mitigate tau-mediated neurotoxicity, supporting the development of peptide-based therapeutics for AD and tauopathies.

Disclosures: M. Hasan: None. **A. Franco:** None. **K. Abd-ElRaouf:** None. **D. Murphy:** None. **J. Zeng:** None. **C. Lo:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.04

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

Support: NIH R01AG092683
NIH R61AG094667
NIH AG063519
NIH AG073082
Dolby Family
NOMIS Foundation Fellowship Program
NIH 1S10OD028511-01

Title: Tau reduction counteracts transcriptomic and behavioral abnormalities in an Alzheimer amyloid model

Authors: *S. J. KNOWLES[1], C. SANT[1], P. NAMBIAR[3], R. A. GONÇALVES[2], K. HO[1], G.-Q. YU[1], R. THOMAS[2], M. MORI[1], V. HUANG[1], S. R. MILLER[4], R. CORCES[3], J. J. PALOP[5], L. MUCKE[3];
[1]Gladstone Inst. of Neurolog. Dis., [2]Gladstone Inst., San Francisco, CA; [4]Gladstone Inst. of Neurolog. Dis., [3]Gladstone Inst. of Neurolog. Dis., San Francisco, CA; [5]Gladstone Inst. & UCSF, South San Francisco, CA

Abstract: Alzheimer’s disease (AD) causes immune dysfunctions, loss of body weight, synapse loss, and behavioral abnormalities. 5xFAD transgenic mice simulate all of these alterations, although they do not develop neurofibrillary tangles. Here we genetically reduced levels of the microtubule-associated protein tau in 5xFAD mice. Using an unsupervised machine learning algorithm, we identified robust behavioral alterations in 5xFAD mice that were prevented or minimized by tau reduction. Tau reduction also preserved presynaptic terminals in the hippocampus and prevented loss of body weight and aberrant plasma cytokine elevations, without changing amyloid burdens or the expression of other microtubule-binding proteins. Single-nucleus transcriptomic analysis revealed that tau reduction broadly counteracts gene expression changes caused by mutant APP and PS1 across multiple types of brain cells,

including and particularly certain populations of excitatory neurons.
Tau reduction was well tolerated in aged Non-Tg mice, in which it did not alter body weight, behavior, or synapse density. Our snRNA-seq analysis enabled us to evaluate the cell type-specific levels of many relevant genes and demonstrated an absence of compensatory increases in the expression of microtubule-associated and tubulin genes after tau reduction.
Together, these findings highlight the importance of nonfibrillar tau in enabling gene expression changes and brain dysfunction triggered by AD-mutant APP and PS1 *in vivo*. They further support the potential benefits of overall tau reduction and illustrate the utility of machine learning-assisted behavioral phenotyping for the detection of brain dysfunctions and AD-related therapeutic interventions.

Disclosures: S.J. Knowles: None. **C. Sant:** None. **P. Nambiar:** None. **R.A. Gonçalves:** None. **K. Ho:** None. **G. Yu:** None. **R. Thomas:** None. **M. Mori:** None. **V. Huang:** None. **S.R. Miller:** None. **R. Corces:** None. **J.J. Palop:** None. **L. Mucke:** F. Consulting Fees (e.g., advisory boards); Biogen, Arvinas.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.05

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

Support: THOME Grant

Title: Pharmacological and ASO-mediated targeting of LRRK2 kinase activity in tau/APOE mouse models of tauopathy and neuroinflammation

Authors: *S. WANG, M. KATYAL, A. B. WEST;
Duke Univ., Durham, NC

Abstract: LRRK2 is a protein kinase genetically linked to Parkinson’s disease and immune-mediated disorders, with emerging roles in endolysosomal trafficking, lysosomal biology, and inflammatory responses in myeloid cells. LRRK2 phosphorylates a subset of Rab GTPases, including Rab10 at threonine 73, a modification that is strongly reduced by LRRK2 kinase inhibition or LRRK2 knockdown. Although LRRK2 has not been established as a primary Alzheimer’s disease risk gene, tau pathology is common in LRRK2 mutation carrier brains, and increased phosphorylated Rab10 has been reported in Alzheimer’s disease brain tissue. These observations raise the possibility that LRRK2 activity may modify tau-associated neurodegeneration and neuroinflammation, but LRRK2-targeting therapeutics have not been rigorously tested in rodent tauopathy models. To address this gap, we evaluated two complementary LRRK2-targeting strategies in P301S human tau mice expressing human APOE alleles. Beginning at six months of age, tau/APOE2 and tau/APOE4 mice were treated with either brain-penetrant small molecule LRRK2 kinase inhibitor PFE-360 administered in chow, or

third-generation LRRK2-targeting antisense oligonucleotides delivered by intracerebroventricular bolus injection. Control cohorts received matched chow or control ASO. Treatment continued through nine months of age, a stage associated with robust tau pathology, neurodegeneration, and neuroinflammatory changes in this model. Primary endpoints include LRRK2 target engagement measured by pT73-Rab10, neurodegeneration, and markers of neuroinflammation. Longitudinal serum biomarkers, including neurofilament light chain, human pTau-181, and pT73-Rab10/total Rab10, are being collected to relate peripheral biomarker trajectories to terminal neuropathological endpoints. These studies are designed to determine whether reducing LRRK2 kinase activity or LRRK2 expression modifies tau burden, neuronal loss, and neuroinflammatory responses in APOE-defined tauopathy models. The results will help clarify whether LRRK2-targeting therapeutic strategies, now clinically advanced in Parkinson's disease, warrant further investigation for tau-associated neurodegenerative disease.

Disclosures: S. Wang: None. **M. Katyal:** None. **A.B. West:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.06

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

Support: Alzheimer's Association Research Grant (25AARG-1375299)

Title: Lysosome-acidifying nanoparticles with BBB-penetrating capability mitigate tau-driven neurotoxicity and neurodegenerative pathology

Authors: *C. LO, Y. ZHONG, D. MURPHY, K. ABD-ELRAOUF, Y. LIU, J. ZENG; Syracuse Univ., Syracuse, NY

Abstract: Alzheimer's disease (AD) and related tauopathies are characterized by tau aggregation, lysosomal dysfunction, and progressive neuronal loss. A central pathological feature of these disorders is lysosomal alkalization, which impairs proteolytic activity, disrupts autophagic clearance, and promotes tau accumulation. Restoring lysosomal acidification therefore represents a promising therapeutic strategy; however, effective delivery to the brain remains challenging because of the blood-brain barrier (BBB). To overcome this limitation, we developed BBB-penetrating acidic nanoparticles (BBB-AcNPs) designed to restore lysosomal pH in central nervous system (CNS) cells. In SH-SY5Y cells expressing tauP301S and human induced pluripotent stem cells (iPSC)-derived neurons harboring tauP301S mutation, tau induced lysosomal alkalization, autophagy defect, mitochondrial dysfunction, and neuronal death. Treatment with BBB-AcNPs restored lysosomal acidification, improved autophagic flux, reduced tau accumulation, and rescued tau-mediated neurotoxicity. We next evaluated BBB-AcNPs in tauP301S (PS19) mice, which exhibit downregulation of vacuolar (H+)-ATPase subunits at both the mRNA and protein levels, consistent with lysosomal dysfunction and

defective autophagy. We confirmed that intravenously administered BBB-AcNPs localized to lysosomes in CNS cells throughout the mouse brain. Treatment of BBB-AcNPs alleviated lysosomal and autophagic defects, reduced tau pathology, and improved cognitive function in tauP301S mice. Together, these findings establish BBB-AcNPs as a promising therapeutic strategy for restoring lysosomal acidification in the brain and as a potential novel treatment of AD and related tauopathies.

Disclosures: C. Lo: None. **Y. Zhong:** None. **D. Murphy:** None. **K. Abd-ElRaouf:** None. **Y. Liu:** None. **J. Zeng:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.07

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant K01AG050719
NIH Grant R01AG068330
BrightFocus Foundation A20201775S
Cure Alzheimer's Fund
R01AG060056
R01AG062550
R01AG080589

Title: Microglial lactate metabolism links amyloid pathology and neuroinflammation in Alzheimer's disease

Authors: *C. C. ASHLEY[1], N. J. CONSTANTINO[2], A. SNIPES[3], E. M. NEARY[3], C. M. KARCH[4], L. A. JOHNSON[3], J. M. MORGANTI[2], S. L. MACAULEY[1];
[1]Physiol., [2]Neurosci., [3]Univ. of Kentucky, Lexington, KY; [4]Psychiatry, Washington Univ. In St Louis, Saint Louis, MO

Abstract: Alzheimer's disease (AD) is increasingly recognized as a disorder of early immunometabolic dysfunction, yet exactly how amyloid-β (Aβ) pathology reshapes brain metabolism and how that metabolic impairment shapes pathogenesis remains poorly understood. Although late-stage disease is associated with cerebral hypometabolism, recent evidence suggests that amyloid pathology initially drives hypermetabolic changes, specifically involving the glycolytic end product lactate. The drivers and consequences of these early metabolic adaptations, however, remain unclear. This project aims to characterize brain lactate metabolism relative to amyloid plaques in the APP/PS1 mouse model and human AD tissue and test whether blocking lactate metabolism alters Aβ-related pathology, metabolism, and neuroinflammation. We found that amyloid plaque deposition is associated with progressive increases in brain lactate in APP/PS1 mice. *In vivo* microdialysis demonstrated that interstitial fluid (ISF) lactate increases

by 50% while ISF glucose decreases by 25% with plaques. Stable isotope-resolved metabolomics revealed widespread metabolic reprogramming characterized by enhanced glycolysis and reduced tricarboxylic acid (TCA) cycle intermediates and neurotransmitter biosynthesis. Lactate dehydrogenase A (Ldha), the enzyme required for lactate generation, is highly enriched in the peri-plaque microenvironment and preferentially localized to diffuse Aβ deposits rather than the dense core of amyloid plaques. Spatial and transcriptomic analyses identified microglia as a major source of lactate within the amyloid-bearing brain; specifically, Ldha is enriched within peri-plaque microglia in APP/PS1 mice. Furthermore, single-cell and single-nucleus transcriptomic analyses reveal upregulated *LDHA* in microglia from clinical AD patients, particularly in a distinct microglial population associated with innate immune signaling and cytokine production. Critically, this immunometabolic signature was reversible. Pharmacological inhibition of lactate dehydrogenase in APP/PS1 mice with stiripentol, an FDA-approved anti-seizure medication, reduced ISF lactate and Aβ levels and selectively depleted peri-plaque microglia, including $Cd68^{+}$ and $Clec7a^{+}$ populations. Ongoing studies are further characterizing the effects of Aβ pathology on microglia mitochondrial function and investigating the functional role of microglial-derived lactate utilizing a novel microglia-specific *Ldha* knockout mouse. These data support a model in which microglial lactate links altered brain metabolism to neuroinflammation and amyloid pathology.

Disclosures: C.C. Ashley: None. **N.J. Constantino:** None. **A. Snipes:** None. **E.M. Neary:** None. **C.M. Karch:** None. **L.A. Johnson:** None. **J.M. Morganti:** None. **S.L. Macauley:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.08

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01-AG028271

Title: Pre-Surgical Voluntary Exercise Attenuates Post-Operative Cognitive Dysfunction and Improves Hippocampal Mitochondrial Respiration in 3xTg-AD Mice

Authors: *J. BLACKWELL[1,4], S. MACKEY-ALFONSO[1,4], B. ALVAREZ[1,4], D. KOLONAY[2,1], H. SANDERS[2,1], K. K. BASKIN[2,1], R. M. BARRIENTOS[3,4];
[2]Physiol. and Cell Biol., [3]Psychiatry and Behavioral Hlth., [1]The Ohio State Univ., Columbus, OH; [4]Inst. of Brain, Behavior and Immunol., Columbus, OH

Abstract: Post-operative cognitive dysfunction (POCD) is the persistent form of post-operative delirium, a noticeable deterioration in cognitive abilities that occurs abruptly following surgery. POCD has been largely associated with older individuals, posing an increased risk for the

development of Alzheimer's disease (AD). Emerging evidence suggests that pre-operative lifestyle factors, including exercise, may influence susceptibility to POCD and AD. It is known that laparotomy (exploratory abdominal surgery) combined with opioid treatment (for pain management) in aged rats produces memory impairments lasting at least 8 weeks, alongside region specific mitochondrial dysfunction. Thus, the purpose of this study was to utilize an acute bout of exercise to mitigate POCD in a mouse model of AD. Mice underwent 3 weeks of voluntary wheel running prior to surgery and morphine. Laparotomies were performed on 3xTg-AD mice at 9 months old followed by 7 days of morphine administration (2mg/kg, i.p., based on our previous work in rats). A battery of cognitive behavioral tests were performed 2 weeks post-surgery. Our findings demonstrated that exercise ameliorated impairments in prefrontal cortex-dependent executive function and hippocampal-dependent memory assessed by nesting and the contextual fear test, respectively. These behavioral improvements were accompanied by a notable decrease in amyloid beta (AB_{42}) in the hippocampus of the exercise + morphine-treated mice compared to sedentary controls. We then examined mitochondrial function in freshly isolated mitochondria from hippocampus using the Seahorse Analyzer XFe96. Exercise + morphine-treated mice demonstrated a significant increase in basal and maximal respiration compared to the sedentary + morphine-treated mice, indicating a rescue in mitochondrial function. These findings suggest that exercise could be used as a non-pharmacological tool prior to surgery to mitigate POCD, potentially through preservation of mitochondrial function.

Disclosures: J. Blackwell: None. **S. Mackey-Alfonso:** None. **B. Alvarez:** None. **D. Kolonay:** None. **H. Sanders:** None. **K.K. Baskin:** None. **R.M. Barrientos:** None.

Nanosymposium

NANO01: Alzheimer's Disease Therapeutic Strategies: Amyloid, Tau, and Metabolism

Location: WCC Rm 145

Time: Saturday, November 14, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO01.09

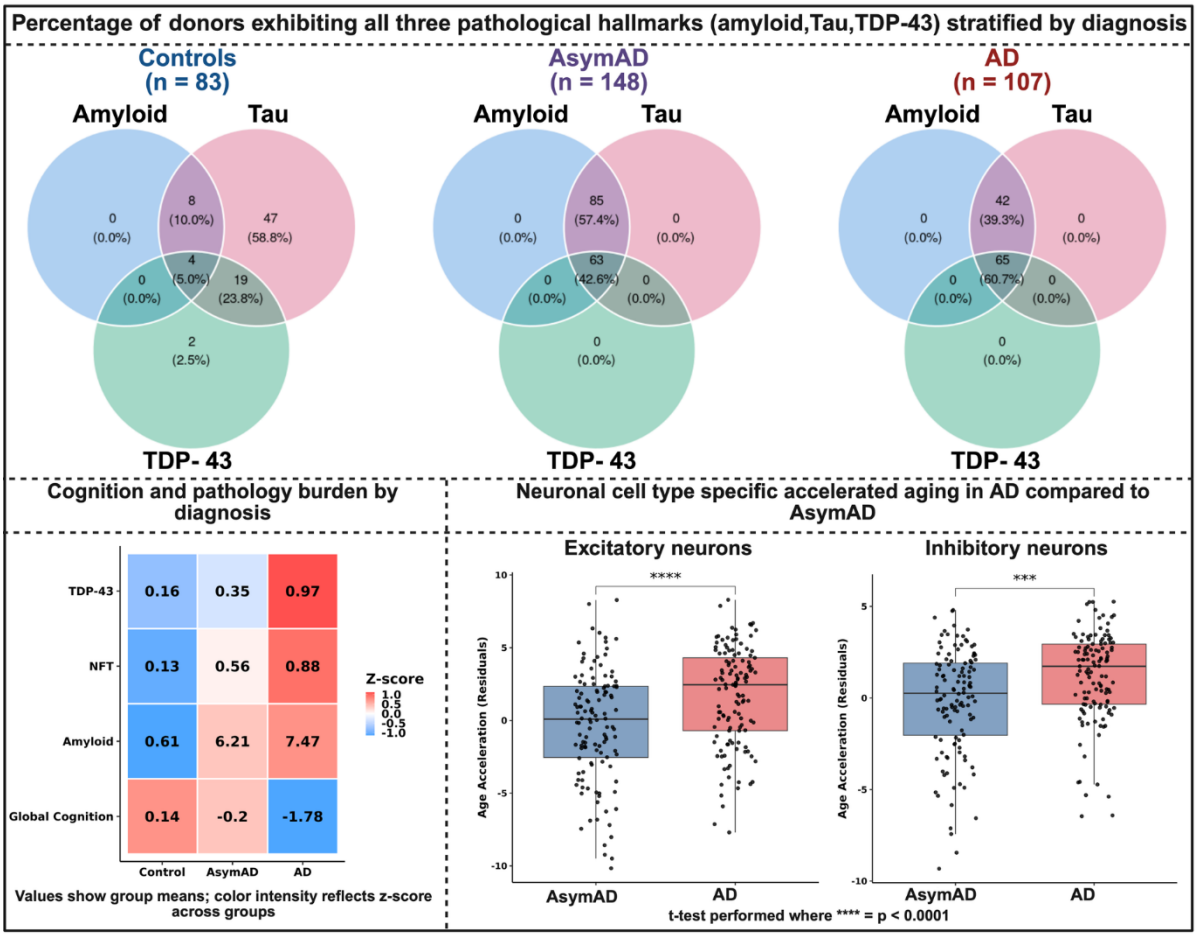
Topic: C.01. Brain Wellness and Aging

Title: Bioenergetic resilience restricts co-pathology and maintains cognition in asymptomatic Alzheimer's Disease

Authors: *P. MANDAL, P. BALONI;
Purdue Univ., West Lafayette, IN

Abstract: Introduction: Alzheimer's disease (AD) remains the leading cause of dementia, yet therapies targeting amyloid-β and tau have shown limited success in restoring cognition. Asymptomatic Alzheimer's disease (AsymAD) individuals exhibit neuropathology comparable to symptomatic AD but maintain cognitive function, suggesting endogenous protective mechanisms. In addition to amyloid-β and tau, up to half of AD cases exhibit TDP-43 co-pathology associated with accelerated cognitive decline but largely absent in AsymAD. The mechanisms underlying cognitive resilience and resistance to TDP-43 co-pathology remain poorly understood.

Methods and Results: To identify protective mechanisms in AsymAD, we integrated proteomic, metabolomic, and single-cell transcriptomic datasets from human postmortem brains (ROSMAP and SEA-AD cohorts) across cognitively normal controls (n = 83), AsymAD (n = 148), and AD (n = 107) cases. Proteomic analyses identified enrichment of mitochondrial bioenergetics (NDUFAF7), protein translation (RPL11), and endosomal trafficking (EEA1) in AsymAD. In contrast, AD brains exhibited elevated neuroinflammatory and disease-associated proteins, including SMOC1 and GPNMB. Metabolomic profiling showed accumulation of short-chain acylcarnitines in AD, consistent with impaired mitochondrial metabolism, whereas AsymAD brains displayed increased neuroprotective metabolites including N-acetylaspartylglutamate and homocarnosine. We integrated single-cell data with transcriptomic aging clocks and identified accelerated biological aging in excitatory and inhibitory neurons in AD vs AsymAD brains. Conclusions: We developed computational workflows integrating multi-omics postmortem brain data and identified preserved mitochondrial function, enhanced cellular maintenance pathways, and delayed neuronal aging as contributors to cognitive resilience in AsymAD. Targeting these protective mechanisms offers therapeutic opportunities beyond amyloid and tau reduction to preserve cognition and limit dementia-associated co-pathologies.



Disclosures: P. Mandal: None. **P. Baloni:** None.

Nanosymposium

NANO02: Auditory Perception and Cognition in Humans and Animals

Location: WCC Rm 146C

Time: Saturday, November 14, 2026, 1:00 PM - 4:15 PM

Presentation Number: NANO02.01

Topic: E.05. Auditory and Vestibular Systems

Title: Altered sound perception and auditory cortical processing in mouse models of autism spectrum disorder

Authors: *N. BARAM[1], T. LEVY[1], A. TEMNOGOROD[1], J. RESNIK[1,2];
[1]Life Sci., Ben Gurion Univ., Be'er Sheva, Israel; [2]Zelman center for Neuroscience, Sch. of Brain Sci., Ben-Gurion Univ., Be'er Sheva, Israel

Abstract: Altered auditory perception is one of the most prominent sensory features of autism spectrum disorder (ASD), yet the circuit mechanisms underlying these perceptual changes remain unclear. Here, we combine in vivo two-photon calcium imaging with behavioral assays in mouse models of ASD to investigate how autism-associated circuit changes shape auditory processing and perception. To examine auditory perceptual differences, mice were tested in a two-alternative forced choice (2AFC) loudness discrimination task. Remarkably, sounds typically classified as ‘soft’ by WT mice were more frequently perceived as ‘loud’ by ASD mouse models. To probe the mechanisms underlying this altered auditory perception, we recorded auditory cortex activity in awake mice during the presentation of sounds at different intensities (N=22 mice, n=2,033 cells). We found that ASD mouse models exhibit altered spontaneous (One-way ANOVA, $F= 63.36$, $p < 0.01$) and sound-evoked activity (Two-way ANOVA, $F = 5.51$, $p < 0.01$) in the auditory cortex as well as changes in auditory adaptation rate and magnitude, compared to wild-type (WT) controls. Consistent with these findings, ASD mouse models also exhibited different trial-to-trial response variability, providing further insight into the observed alterations in auditory perception. These cortical findings allowed us to develop a model in which altered spontaneous activity, sound-evoked responses, adaptation dynamics, and trial-to-trial variability reshape auditory cortical gain, biasing ASD mouse models toward increased loudness perception. Together, our results provide a mechanistic framework for understanding auditory hypersensitivity in ASD and suggest that disrupted cortical gain control may contribute to the atypical sensory perception.

Disclosures: N. Baram: None. **T. levy:** None. **A. Temnogorod:** None. **J. Resnik:** None.

Nanosymposium

NANO02: Auditory Perception and Cognition in Humans and Animals

Location: WCC Rm 146C

Time: Saturday, November 14, 2026, 1:00 PM - 4:15 PM

Presentation Number: NANO02.02

Topic: E.05. Auditory and Vestibular Systems

Title: Dynamic of stress-induced changes in auditory processing and perception

Authors: *L. DOR[1,2], J. RESNIK[1,2];
[1]Life Sci., Ben-Gurion Univ., Be'er Sheva, Israel; [2]Zelman Ctr. for Neuroscience, Sch. Of Brain Sci. and Cognition, Ben-Gurion Univ., Be'er Sheva, Israel

Abstract: Stress rapidly reshapes brain state, but how these changes affect sensory cortical processing remains largely unknown. Although prolonged stress impairs auditory processing and perception, the dynamics of auditory cortical activity during acute stress and recovery are poorly understood. Here, we examined how acute stress modulates auditory cortical processing in awake mice using longitudinal two-photon calcium imaging combined with pupillometry, providing an independent readout of the physiological stress response. To characterize the effects of acute stress on auditory cortical processing, we imaged auditory cortex activity across baseline, acute stress, and recovery sessions (N = 4 mice, n = 971 registered cells). Acute stress produced dynamic changes in cortical activity: sound-responsive neurons showed reduced spontaneous and sound-evoked responses during stress, followed by partial recovery after the stress period. Stress also shifted the onset-to-offset response ratio, suggesting altered temporal response structure. At the population level, acute stress reorganized network coordination, including changes in noise correlation structure. Pupillometry revealed marked inter-individual variability in stress susceptibility and a state-dependent relationship between physiological stress responses and cortical activity changes (Pearson correlation, $r = 0.98$, $p = 0.023$). Consistent with these circuit-level changes, population decoding showed impaired sound-intensity discrimination during stress, particularly for small intensity differences. Together, these findings indicate that acute stress rapidly reshapes auditory cortical processing across single-neuron, network, and decoding levels, with potential consequences for sound perception.

Disclosures: L. Dor: None. **J. Resnik:** None.

Nanosymposium

NANO02: Auditory Perception and Cognition in Humans and Animals

Location: WCC Rm 146C

Time: Saturday, November 14, 2026, 1:00 PM - 4:15 PM

Presentation Number: NANO02.03

Topic: E.05. Auditory and Vestibular Systems

Support: Penn Provost Postdoctoral Fellowship
NIH R01 DC014479

Title: Pupil-linked arousal shapes sound encoding in populations of auditory thalamic neurons

Authors: *A. DROTOS, R. BALAJI, M. LIU, M. SCHNEIDER, M. N. GEFFEN;
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Abstract: The primary role of sensory systems in the brain is to generate representations of sensory objects that guide behavior. In the auditory system, neurons encode sound features through changes in firing rate and timing, forming neuronal representations that evolve as information ascends from the cochlea to the cortex. However, sound representations in the auditory system cannot be fully determined by acoustic features alone. Neuronal responses instead exhibit substantial trial-to-trial variability even for identical sounds, suggesting that auditory representations are shaped by latent internal variables such as arousal state that modulate sensory encoding. As the primary thalamic relay between the auditory periphery and cortex, the medial geniculate body (MGB) is well positioned to integrate sensory input with internal state. To examine how internal state shapes sound representations in MGB, we used Neuropixels probes to simultaneously record small populations of neurons in awake, head-fixed mice while measuring pupil size as an index of arousal and locomotion on a self-propelled treadmill. Across the population, models including pupil size and/or locomotion significantly improve predictions of neuronal activity, with many neurons sensitive to one or both variables. In addition, sound frequency tuning becomes more selective at intermediate arousal levels, reflected in increased FRA sparseness without systematic shifts in best frequency. In contrast, rate coding of amplitude-modulated sounds appeared comparatively stable across arousal states. Beyond changes at the level of individual neurons, we also found that arousal state reshapes population-level representations of sound across simultaneously recorded MGB neurons. Together, these results demonstrate that auditory thalamic coding is dynamically regulated by internal state, suggesting a key role for the auditory thalamus in adaptive sensory processing.

Disclosures: A. Drotos: None. **R. Balaji:** None. **M. Liu:** None. **M. Schneider:** None. **M.N. Geffen:** None.

Nanosymposium

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Location: WCC Rm 146C

Time: Saturday, November 14, 2026, 1:00 PM - 4:15 PM

Presentation Number: NANO02.04

Topic: E.05. Auditory and Vestibular Systems

Support: Overseas Postgraduate Education Scholarship, MEB (Republic of Turkey Ministry of National Education)

Title: Context Precision Modulates Neural and Pupillary Responses: An EEG and Eye Tracking Experiment

Authors: *B. ADAM, M. CHAIT;
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Abstract: The brain continuously generates predictions about incoming sensory input and updates its internal models when those predictions are violated. Because sensory inputs are inherently uncertain, not all prediction errors require model updating; instead, their impact may depend on the precision (or confidence) assigned to the current predictive model. Here, we investigated how model-derived estimates of uncertainty and confidence shape neural and pupillary responses to changes in auditory sequence statistics. In a combined EEG-pupillometry experiment, we recorded brain activity and pupil responses while participants (n=40) listened to rapid tone sequences. Stimuli had transitions between different statistical structures, with novel frequencies introduced at the transition. We found that both EEG and pupil responses track the changes in sequence statistics. To characterise trial features, we used two models, PPM (Pearce, 2005) and DREX (Skerritt-Davis & Elhilali, 2018), representing different hypotheses about the brain's statistical tracking (Markov chain vs Bayesian). We quantified trial-wise entropy (PPM) and precision (D-REX) to reflect sequence uncertainty and confidence, then examined how EEG and pupil responses varied based on these measures. Trials were then median-split into high- and low-value groups for each metric, and associated EEG and pupil responses were compared. Neural responses revealed that transition-evoked activity varied systematically with context precision, with more precise contexts eliciting later transition-evoked responses. In addition, pupil responses exhibited both sustained and transition-evoked differences. During the pre-transition interval, high-precision sequences were associated with smaller sustained pupil responses than low-precision sequences, reflecting reduced processing demands under more predictable conditions. Following the transition, high-precision sequences elicited a phasic pupil dilation, whereas low-precision sequences evoked a rapid pupil constriction, suggesting distinct neuromodulatory mechanisms to track changes in sequence statistics as a function of context precision. Notably, computational characterisation revealed differences in both neural and pupil responses even within otherwise identical stimuli. In contrast, entropy estimates derived from PPM did not vary with either neural or pupil responses. Overall, these findings suggest that auditory processing is linked to Bayesian estimates of precision, highlighting the influence of context precision on neural and pupillary responses to changes in auditory regularities.

Disclosures: B. Adam: None. **M. Chait:** None.

Nanosymposium

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Location: WCC Rm 146C

Time: Saturday, November 14, 2026, 1:00 PM - 4:15 PM

Presentation Number: NANO02.05

Topic: E.05. Auditory and Vestibular Systems

Title: Communicative context modulates frontal cortex activity during marmoset vocal production

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Abstract: Marmoset vocal communication consists of dynamic, context-dependent exchanges with conspecifics. Previous work has shown that single-unit and LFP activity in the frontal cortex is modulated during vocal production, but it remains unclear whether this activity also reflects the communicative context preceding a call-that is, whether the frontal cortex represents the recent vocal input rather than simply reflecting motor output. We investigated this question by analyzing the conspecific vocalizations perceived before vocal production in two freely moving marmosets engaged in vocal interactions. We focused on high-gamma activity for trill call production. For each produced trill, we extracted two parameters describing the communicative context in the seconds before call onset—ambient vocal activity, the overall level of vocal activity in the room preceding the call (capturing whether the animal was in a busy vocal interaction or relative silence), and perceived trill duration, the total duration of trills from other marmosets in the 5s preceding production (capturing whether the call was likely part of an ongoing trill exchange). Both parameters were behaviorally relevant, influencing the likelihood and timing of the animal's vocal production. We also extracted two parameters describing the produced call itself—its duration and mean frequency. To test whether context shapes neural activity, we used a sliding-window linear encoding model that predicted high gamma power from all four parameters at each time point relative to call onset. To isolate each parameter's unique contribution, we computed its unique R^2 and tested it against a shuffled null. We found that both context parameters contributed unique variance to high gamma power around the onset of produced calls. Rather than reflecting a sustained representation of the environment, this context encoding is built in the seconds before call onset. Across the recorded regions, context and production encoding appeared to be spatially intermixed rather than segregated. Together, these results suggest that frontal cortex activity during vocal production carries information about the surrounding communicative context in addition to the motor production of the call, and that the frontal cortex may contribute to communication not only by driving motor output but by integrating prior vocal-acoustic context.

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Nanosymposium

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Presentation Number: NANO02.06

Topic: E.05. Auditory and Vestibular Systems

Support: Marie-Josée and Henry R. Kravis Foundation
NIDCD R01

Title: World Models as a Neurocomputational Bridge Between Action and Perception For Large Scale Electrocorticography Data

Authors: *R. J. ANTONELLO[1], A. KHALILIAN-GOURTANI[4], G. MISCHLER[2], W. K. DOYLE[6], D. FRIEDMAN[7], A. FLINKER[5], N. MESGARANI[3];

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Abstract: Recent advances in machine learning have allowed researchers to build complex models of how the brain processes auditory, visual and language stimuli. These models have provided new insights into the nature of how these multifarious representations are encoded in the brain, yet they are often limited in that they often focus on narrowly tailored naturalistic tasks such as movie watching or story listening. In this work, we use a vast, multi-day electrocorticograhy dataset with paired audiovisual data of subject behavior to create a new paradigm of multimodal brain models that can richly capture the complex interplay between stimulus, neural representation, and behavior in arbitrary settings. Crucially, we pioneer the use of pretrained world models as generalist models that can effectively embed the vast landscape of potential human behaviors and actions. We train a model with a contrastive loss objective that allows us to learn a shared embedding space for externally observable human actions and neural representations in motor and auditory cortex. Finally, we demonstrate that the model we build can expressively capture how behavioral context can modulate the auditory processing pipeline in complex scenarios like natural conversation.

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Nanosymposium

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Presentation Number: NANO02.07

Topic: E.05. Auditory and Vestibular Systems

Title: Experience-dependent AMPAR dynamics organize hierarchical auditory-language cognition in the human brain

Authors: *T. SAHARA[1], H. ABE[2], W. NAKAJIMA[3], M. HATANO[3], S. TSUGAWA[3], A. KASHIO[4], Y. ARAI[3], N. ORIDATE[3], K. KONDO[4], T. TAKAHASHI[3];
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Abstract: Introduction How molecular synaptic plasticity contributes to adaptive reorganization of human cognitive networks remains poorly understood. Cochlear implants (CIs) restore auditory input through a spectrally impoverished signal, requiring recipients to adapt over months through a learning-like rehabilitation process. This provides a unique human model for studying experience-dependent plasticity during recovery of auditory-language function. AMPA receptors (AMPARs) are central mediators of synaptic plasticity, yet direct evidence for such mechanisms in the living human brain has been limited. Here, we used [^{11}C]K-2 PET, which

visualizes cell-surface AMPARs, to test whether AMPAR dynamics accompany hierarchical speech-network reorganization after CI. **Methods** Thirty adults with acquired bilateral severe-to-profound hearing loss underwent [11C]K-2 PET before and 6 months after CI. SUVR images were analyzed using whole-brain normalization for relative redistribution and white-matter referencing for brain-wide AMPAR density. Voxel-wise paired analyses tested postoperative AMPAR changes, and voxel-wise regressions examined associations between AMPAR changes and improvements in monosyllable, word, sentence, and monosyllable-in-noise perception. Preoperative AMPAR availability was tested as a predictor of speech outcomes using multivariable models. **Results** Compared with healthy controls, AMPAR density was elevated in hearing loss and decreased after implantation toward the healthy-control range. Whole-brain-normalized analysis revealed a selective relative increase in the left posterior superior/middle temporal region, near classical auditory-language cortex, with relative decreases in parietal regions. Speech-perception improvements were positively associated with AMPAR increases in higher-order cortical regions, with no negative correlation regions. Correlation maps suggested a nested hierarchy: broad regions associated with monosyllabic recovery converged toward more restricted systems associated with word and sentence recovery. Monosyllable-in-noise recovery additionally involved bilateral frontal regions, consistent with attentional control during degraded speech perception. Preoperative cerebellar AMPAR availability predicted 6-month monosyllable outcome after adjustment for age, deafness duration, and preoperative speech perception. **Conclusions** CI-induced auditory-language recovery is accompanied by AMPAR reorganization in the human brain. These findings suggest that experience-dependent AMPAR dynamics support hierarchical recovery after sensory restoration.

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Nanosymposium

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH/NIDCD Grant R01DC018523
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Title: Functional Neural Activity and Connectivity Deficits Underlying Vocal Auditory Feedback Control in Post-stroke Aphasia: An fMRI Study

Authors: *R. BEHROOZMAND[1], J. VENEZIA[2], K. SARMUKADAM[3], C. RORDEN[4], L. BONILHA[5], G. S. HICKOK[7], J. FRIDRIKSSON[6];
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[5]Neurol., [6]Communication Sci. & Disorders, Univ. of South Carolina, Columbia, SC; [7]Univ. California, Irvine, CA

Abstract: Aphasia is a consequence of left-hemisphere stroke characterized by speech-language impairments. Aphasia treatments primarily focus on motor speech outcomes, with limited attention to the role of sensory feedback integration in speech rehabilitation. This project takes a key step toward refining treatment strategies by focusing on how auditory feedback processing deficit disrupts vocal production and motor control. We collected fMRI data in 15 aphasia and 15 matched controls while they vocalized speech vowel sounds and listened to playback of their own voice under pitch-shifted (±100 cents) altered auditory feedback (AAF). Aphasia group exhibited reduced AAF compensatory responses, reflecting impairments in feedforward and feedback-based vocal control mechanisms. Stroke-induced brain damage in aphasia was associated with reduced activation within left-hemisphere dorsal stream network, including premotor and motor cortices, posterior superior temporal gyrus (pSTG), and supramarginal gyrus (SMG). Functional connectivity analyses revealed weakened coupling between pSTG and dorsal and ventral precentral speech areas, indicating disrupted auditory-motor integration. Although connectivity strength did not directly predict maladaptive vocal behavior, significant group-dependent brain-behavior associations emerged within precentral speech areas. In controls, greater bilateral ventral and right-lateralized dorsal precentral activity was associated with smaller compensatory responses, whereas in aphasia this relationship was reversed and right-lateralized. Together, these findings provide converging evidence of disrupted auditory-motor integration and functional reorganization of right-hemisphere neural mechanisms in aphasia. Our findings suggest that aphasia interventions may benefit from targeting sensorimotor mechanisms supporting auditory feedback processing and control. Personalized interventions that engage or strengthen contralesional sensorimotor pathways could further enhance recovery of fluent verbal communication.

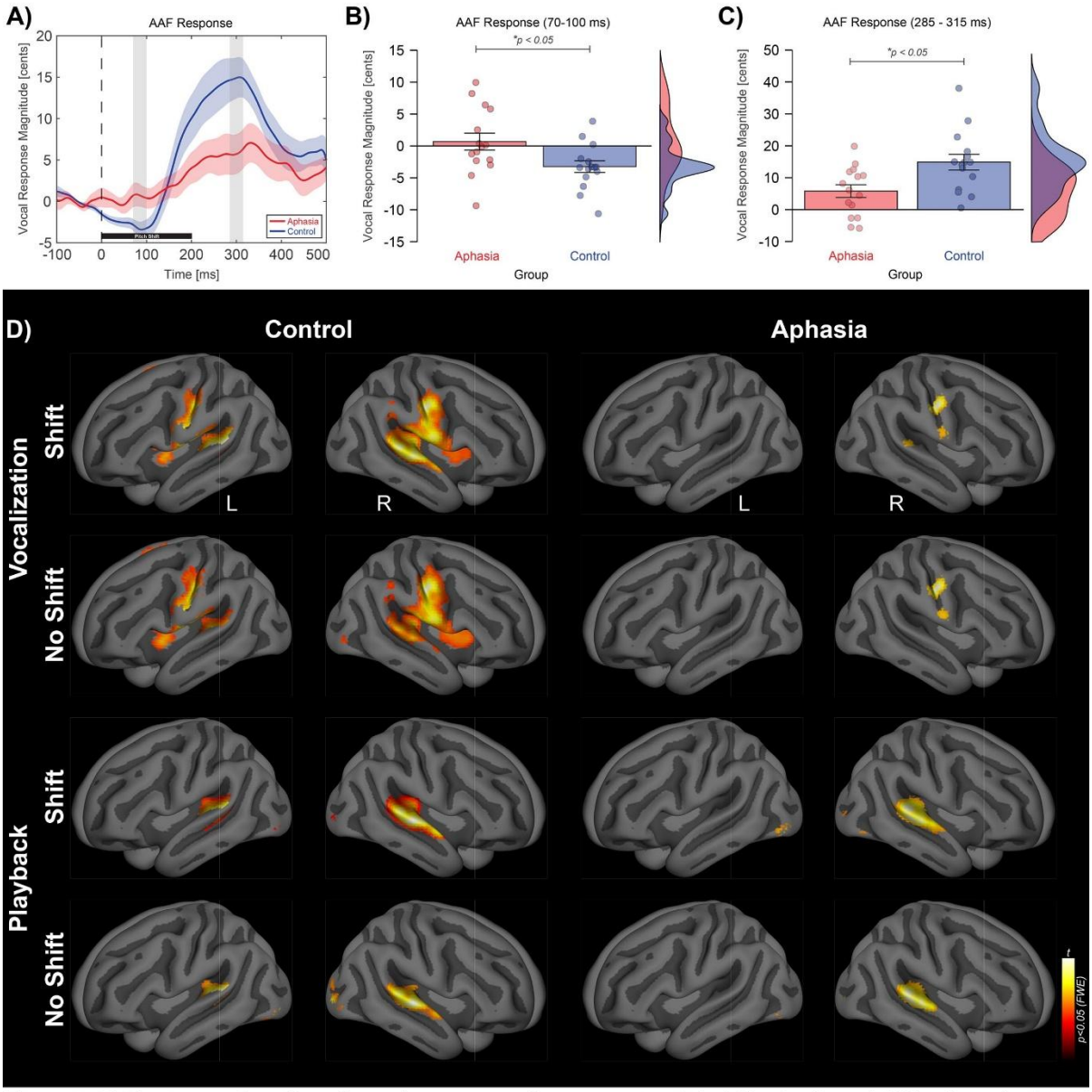


Figure 1. **A)** The temporal profiles of grand-average vocal responses to pitch-shift stimuli overlaid for the aphasia and control groups. **B)** The bar plot and histogram representations of vocal response magnitudes in a time window from 70 – 100 ms for the aphasia and control groups following the onset of pitch-shift stimuli. **C)** The bar plot and histogram representations of vocal compensation peak magnitudes in a time window from 285–315 ms for the aphasia and control groups following the onset of pitch-shift stimuli. In panels B and C, error bars indicate the standard error of the mean (SEM). **D)** The cortical map of significant BOLD responses in the MNI space for the control and aphasia groups during vocalization and playback tasks under pitch-shift and no-shift conditions relative to rest ($t \geq 4.64$, $p < 0.05$, FWE corrected). The color-coded areas represent significant t-values projected onto the smoothed ICBM152 standardized brain template. The letters "L" and "R" indicate left and right hemispheres, respectively.

Disclosures: R. Behroozmand: A. Employment/Salary (full or part-time):; University of Texas at Dallas. 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/NIDCD Grant R01DC018523 (PI). **J. Venezia:** A. Employment/Salary (full or part-time):; VA Loma Linda

Healthcare System, I01-RX005059 (VA RR&D Merit Award). **K. Sarmukadam:** A. Employment/Salary (full or part-time):; University of South Carolina. **C. Rorden:** A. Employment/Salary (full or part-time):; University of South Carolina. 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. **L. Bonilha:** A. Employment/Salary (full or part-time):; University of South Carolina. 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. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SpeakableWellness . **G.S. Hickok:** A. Employment/Salary (full or part-time):; UC Irvine. 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. **J. Fridriksson:** A. Employment/Salary (full or part-time):; University of South Carolina. 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.

Nanosymposium

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Topic: E.05. Auditory and Vestibular Systems

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Title: Single-neuron and population-level encoding of content and time in the human speech cortex

Authors: *A. SARKAR[1,2], S. JAIN[2], Y. NORMAN[2], R. GANDHI[3], S. HU[2], P. PARRAMON-ARCOS[2], M. K. LEONARD[2], E. F. CHANG[2];
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Abstract: Comprehending speech requires mapping acoustics to linguistic representations while tracking sequence structure in time - integrating content ("what") with timing ("when"). Electrocorticography (ECoG) links the superior temporal gyrus (STG) to phonetic processing, yet how single cells integrate this temporal structure with phonetic content is unclear. We recorded >1,500 single neurons via Neuropixels probes in 17 participants listening to sentences, characterizing coding with temporal receptive field (TRF) models and population

representational geometry. At the single-cell level, individual neurons respond to specific sounds only at preferred elapsed times - e.g., firing to approximants (/l/, /r/) only at sentence onset. Here, TRFs combining sound with position explain ~40% of activity, far more than either alone. Another subpopulation forms stable neural sequences across sentences, showing enhanced firing at preferred elapsed times, with more cells active early and firing fields broadening at later latencies, a temporally compressed organization reminiscent of hippocampal time cells (Cao et al., 2022). This temporal organization appears in ECoG high-gamma, revealing a shared compressed code across neuronal scales. Additionally, distinct "lexical boundary" cells exhibit characteristic firing dips at word transitions, providing a candidate single-unit substrate for population-level cortical "resets" observed in mesoscale STG recordings (Zhang et al., 2025). At the population level, PCA reveals that these cellular properties collectively generate trial-averaged, continuous state-space trajectories at distinct timescales - the broader population exhibits sentence-spanning cycles, while lexical boundary cells show only word-scale resets. Interestingly, a highly speech-responsive ensemble (selected for consistent firing across trials) exhibits both: distinct word-level sub-loops emerge within a larger sentence-level scaffold. Crucially, these sub-loops do not return to their origin but advance along the broader trajectory, reflecting a hierarchical code that simultaneously organizes local word structure and global elapsed time. Isomap dimensionality reduction of this ensemble shows a continuous 2D manifold sheet: elapsed time establishes a smooth longitudinal trajectory, while phonetic variance shapes lateral expansion. These results suggest the human STG collectively represents what is said and when, extending temporal-coding principles from the hippocampus to sensory cortex and revealing a low-dimensional representational geometry that systematically organizes content and time during natural speech.

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Nanosymposium

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Topic: E.05. Auditory and Vestibular Systems

Support: MRC MR-T032553-1
NIH R01 DC004290

Title: Single neurons respond to acoustic event boundaries in humans

Authors: *J. I. BERGER[1], A. J. BILLIG[2], H. KAWASAKI[1], Y. MOHAMMADI[2], M. A. HOWARD, III[1], T. D. GRIFFITHS[3];
[1]Univ. of Iowa, Iowa City, IA; [2]Ear Institute, Univ. Col. London, London, United Kingdom; [3]Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: In order to detect changes in the world around us, our brains have to segment constantly changing stimuli. Recent intracranial work utilising visual paradigms has identified cells that signal the transition between visual scenes, highlighting contributions of structures including the hippocampus and amygdala. However, it is not yet clear whether these neurons (or others in the same areas) also process changes in acoustic stimuli or whether these responses are evident in the absence of a behavioural task requiring high-level cognition. Here, we report human intracranial recordings of single neurons recorded from various brain structures while participants performed an auditory boundary detection task. Participants (N = 11) listened to concatenated texture sections, each lasting several seconds and consisting of tone glides randomly overlapping in time and frequency. Glide direction and frequency excursion were fixed within a section, but one or both parameters changed from section to section - thus creating acoustic boundaries that did not vary in their overall energy or spectrum. Participants listened passively to the stimuli and were then required to listen again while detecting boundaries between acoustic events. Single neurons (n = 1163) were isolated offline using an automated procedure with manual curation. Neurosurgical participants performed the task well, detecting boundaries with ~87% accuracy and an average behavioural response latency of ~880 ms. Approximately 10% of all recorded cells in the medial temporal lobe (amygdala, hippocampus and parahippocampal gyrus; n = 502 total recorded) responded during the active detection of acoustic boundaries, with an average latency of ~600 ms. Auditory boundary cells were also evident in the insula and lentiform nucleus. A separate minority of cells (3.8% of all recorded neurons) responded during passive listening, with 13% of passively modulated cells also modulated in the active condition. Overall, we demonstrate the existence of cells in the medial temporal lobe that respond to acoustic boundaries, and these data implicate this region in auditory event segregation.

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Nanosymposium

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Topic: E.05. Auditory and Vestibular Systems

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NIH/NIDCD Award F31DC023124

Title: Perceptual consistency in phoneme categorization is driven by neural consistency and predicts improved speech-in-noise performance

Authors: *R. RIZZI, J. STIRN, Z. EISENHUT, G. M. BIDELMAN;
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Abstract: Background: Listeners discretize the speech signal by assigning sounds to phonetic categories, though there is variability between individuals in how they accomplish categorization. Having more consistent categorization of sounds may be advantageous for understanding speech-in-noise (SIN). It is unclear how different levels of neural processing in the auditory system reflect these perceptual differences. In particular, whether the consistency of subcortical and cortical speech-evoked responses drive perceptual consistency in acoustic-mapping has not been thoroughly explored. **Methods:** We recorded brainstem frequency-following responses (FFRs) and cortical event-related potentials (ERPs) while listeners actively labeled vowels along an acoustic-phonetic continuum using a visual analog scale. We measured individual differences in consistency via phoneme labeling and SIN comprehension via the QuickSIN. We computed intertrial consistency of neural responses to index the stability of listeners' neural speech representation across stimulus presentations. We also assessed how faithfully midbrain and cortical responses represented stimulus acoustics using representational dissimilarity matrices (RDMs) computed across all token pairs. Neural RDMs were then compared with acoustic and phonetic category RDMs to assess whether FFRs and ERPs carried gradient vs. categorical information of the speech signal. **Results:** Greater behavioral consistency during phoneme labeling was correlated with improved SIN scores. Neurally, we found greater cortical or subcortical consistency predicted greater behavioral consistency. RDMs revealed subcortical responses retained more acoustic details, while cortical responses more closely reflected abstract phoneme categories. **Conclusions:** Our findings reveal important benefits of perceptual consistency to several domains of speech perception. We find perceptual consistency is driven by more consistent encoding of speech at either a cortical or subcortical level. More consistent sensory processing could provide a more stable readout of the speech signal to higher cortical brain areas. This could in turn confer advantages to later perceptual processes downstream, including understanding speech in noise.

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Nanosymposium

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Presentation Number: NANO02.12

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC017785

Title: Aging alters orbitofrontal top-down modulation of auditory cortical representations

Authors: *P. GUO, P. O. KANOLD;
Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Age-related hearing difficulties encompass complex sensory and cognitive changes that cannot be fully explained by peripheral hearing loss. Top-down modulation from higher-

order cortical areas can shape sound perception, support context-dependent extraction of auditory information, and influence performance during behaviorally relevant auditory tasks. In this study, we aimed to determine how aging affects OFC (Orbitofrontal Cortex) terminal activity in the primary auditory cortex (A1). We expressed GCaMP6s in OFC projection neurons and performed two-photon calcium imaging of OFC axonal terminals in A1 from adult and aged CBA/Caj mice (~2ys old). To characterize auditory representations in this feedback pathway, we presented tone stimuli across multiple frequencies and varying signal-to-noise ratios (SNRs). We quantified sound response features and found that aging OFC terminals in A1 exhibit robust sound-evoked activity under passive conditions, indicating that OFC terminals still convey sound stimulus related information to A1. However, aging altered multiple features of the auditory stimulus representation in the OFC feedback pathway. We found that, compared to OFC terminals in adult animals, OFC terminals in aging A1 have larger sound evoked response amplitudes, but reduced SNR-dependent response modulation. These results are consistent with weaker contrast extraction of sounds across SNR in the presence of stronger sound-evoked OFC terminal responses. Together, these results suggest that aging does not simply reduce OFC feedback activity but instead alters the gain and selectivity of OFC inputs to auditory cortex. By altering OFC feedback signals in A1, aging may impair the flexibility and context-dependent extraction of auditory information, contributing to age-related hearing difficulties.

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC018353

Title: Vocalizations evoke behavioral responses and recruit specific excitatory and inhibitory neuron ensembles across primary and higher-order auditory cortex

Authors: *Z. GHASEMAHMAD[1], M. THOMAS[2], E. CHIN[1], C. G. SWEENEY[3], J. J. WENSTRUP[4], A. E. TAKESIAN[5];
[1]Mass. Eye and Ear; Harvard Med. Sch., Boston, MA; [2]Mass Eye and Ear, Boston, MA; [3]Mass Eye and Ear/Harvard Med. Sch., Boston, MA; [4]Dept. of Anat. and Neurobio., Northeast Ohio Med. Univ., Rootstown, OH; [5]Otolaryngology, Massachusetts Eye and Ear, Boston, MA

Abstract: Mice produce a rich repertoire of complex vocalizations across diverse behavioral contexts, such as mating and stress. The auditory cortex is positioned to process these vocalizations and relay this information to motor and limbic centers, thereby shaping context-appropriate reactions. However, how vocalizations modulate behavioral state and how they are represented across excitatory and inhibitory cell types within auditory cortex remain unclear.

Using widefield and two-photon calcium imaging in awake head-fixed mice, we measured responses of excitatory and inhibitory auditory cortical neurons to conspecific vocalizations recorded in three contexts — mating, restraint, and isolation. Specific vocalizations evoked robust behavioral responses, including changes in pupil diameter, whisking, and locomotion, which were more pronounced than responses to time-reversed control stimuli. These behavioral responses habituated across repeated presentations of vocalizations but not across repeated presentations of control stimuli. Widefield imaging revealed stronger vocalization-evoked activity in higher-order auditory cortical regions than in primary auditory cortex. At single-cell resolution using two-photon imaging, both excitatory and inhibitory neuronal populations showed selectivity for specific vocalizations, with greater selectivity observed in higher-order cortical regions. Notably, many neurons responded robustly to natural vocalizations but not to synthetic sounds with matched spectral content. Moreover, small ensembles of vocalization-selective excitatory and inhibitory neurons reliably decoded call identity. Ongoing analyses are evaluating how behavioral state and experience modulate the selectivity of these responses. Together, these findings reveal that vocalizations can alter the arousal state of the listener and are encoded by sparse, selective excitatory and inhibitory neuronal ensembles, indicating the contributions of distinct cortical circuits to the encoding of socially relevant acoustic signals.

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Nanosymposium

NANO03: Respiratory Control

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Presentation Number: NANO03.01

Topic: F.08. Respiratory Regulation

Support: R01 HL128970
R01 HL174409
NIH S10OD032420

Title: Leptin augments the hypercapnic ventilatory response (HCVR) via the 5-HT pathway

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Abstract: Rationale: We have previously shown that intranasal (IN) administration of leptin augments the hypercapnic ventilatory response (HCVR) and attenuates inspiratory flow limitation, thereby improving obesity hypoventilation in mice with diet-induced obesity (DIO). We also demonstrated that the respiratory effects of leptin are mediated by neurons of the dorsomedial hypothalamus projecting to the dorsal and medullary raphe nuclei. We hypothesized that intranasal leptin augments HCVR via the 5-HT pathway, and that these effects would be abolished by the 5-HT_2A/2C receptor blocker pimavanserin or by the elimination of 5-HT neurons projecting to the hypoglossal nucleus.
Methods: We used 29 Sert-Flp male mice, in which FlpO recombinase is expressed under the serotonin transporter promoter with DIO (45-50 g of weight). In Experiment 1, we conducted a randomized crossover trial comparing a single dose of IN leptin (0.8 mg/kg) vs. vehicle and subcutaneous pimavanserin (3 mg/kg) vs. placebo in 15 mice (four treatment combinations: leptin + pimavanserin, leptin + placebo, vehicle + pimavanserin, vehicle + placebo), each administered one week apart. Minute ventilation (V_E) was measured during quiet wakefulness at normocapnia and 8% CO_2 in a thermoneutral environment (28-30°C) 30 minutes after each treatment. HCVR was calculated as the slope of V_E versus inspired CO_2 using linear least-squares regression. In Experiment 2, a separate group of DIO Sert-Flp mice received stereotactic injections into the hypoglossal nucleus of either retrograde AAV harboring Flp-dependent caspase (n = 7) or a retrograde AAV-GFP control virus (n = 7). **Results:** In Experiment 1, leptin did not affect V_E under normocapnia but increased minute ventilation under hypercapnic conditions in the absence of pimavanserin. Pimavanserin had no effect on ventilation at normocapnia but markedly attenuated the HCVR regardless of leptin treatment. The combination of leptin and pimavanserin significantly suppressed normocapnic breathing. In Experiment 2, control virus-treated mice showed abundant 5-HT^+ neurons in the medullary raphe (MR) and in the dorsal raphe (DR). Many 5-HT^+ MR neuronal bodies were GFP+ suggesting monosynaptic projections to the hypoglossal nucleus. In contrast, a very few 5-HT+ DR neuronal bodies were GFP+, but we observed abundant GFP+ fibers enmeshing DR neurons Caspase treatment eliminated 5-HT^+ neurons in MR, but not in DR. As in Experiment 1, leptin did not affect baseline ventilation but increased hypercapnic ventilation and HCVR in mice treated with the control virus. Elimination of 5-HT^+ neurons projecting to the hypoglossal nucleus abolished leptin's effects on HCVR.

Disclosures: D. Davaanyam: None. **M. Alexis Ruiz:** None. **J. de Deus:** None. **M. Shin:** None. **X. Wang:** None. **M. Islam:** None. **C. Clarkson:** None. **M.R. Amorim:** None. **A.S. Popratiloff:** None. **D.S. Mendelowitz:** None. **V. Polotsky:** None.

Nanosymposium

NANO03: Respiratory Control

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Topic: F.08. Respiratory Regulation

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Title: Functional Role of Glutamatergic Neurons within the Nucleus of the Solitary Tract in Swallow Pattern Generation

Authors: *A. HUFF, P. NOGUERA GOMEZ, A. SWEENEY;
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Abstract: Oropharyngeal dysphagia exacerbates underlying conditions and increases hospitalization rates in pulmonary, sleep, and neurological disorders. Recent work identified the postinspiratory complex (PiCo), located within the intermediate reticular formation, as a trigger for swallow in a respiratory-phase dependent manner. However, the swallow pattern generator (SPG) has historically been localized to the Nucleus of the Solitary Tract (NTS). This has led to the hypothesis that PiCo contributes to swallow-breathing coordination, while the specific neuronal populations for swallow generation remain unclear. We hypothesize that excitatory neurons within the NTS are necessary for swallow generation. To test this, both male and female Vglut2cre mice were used. A non-pathogenic adeno-associated viruses (AAV) enabling cell-type-specific expression of either channelrhodopsin (ChR2) or inhibitory (hM4Di) DREADDs, was injected into the interstitial (SolI) and intermediate (SolIM) subnuclei of the caudal nucleus of the solitary tract (cNTS). After a 21-day expression period, swallows were elicited in freely breathing, urethane-anesthetized mice by (1) oral water delivery, (2a) optogenetic stimulation of cNTS neurons, and/or (2b) oral water delivery after administration of the DREADD activator, clozapine-N-oxide (CNO). Swallow and laryngeal activity were measured via monopolar suction electrodes of the hypoglossal (XII) and vagus (X) nerves as well as bipolar electromyogram (EMG) of the submental, laryngeal complex, and costal diaphragm muscles. Post-hoc histological analysis confirmed accurate targeting of injection sites. Activation of Vglut2-expressing neurons in the cNTS reliably triggered a swallow, whereas chemogenetic inhibition eliminated swallow production in response to oral water stimulation. These findings support the conclusion that excitatory cNTS neurons are integral components of the SPG and are necessary for swallow generation.

Disclosures: A. Huff: None. **P. Noguera Gomez:** None. **A. Sweeney:** None.

Nanosymposium

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University of Virginia Brain Institute Presidential Fellowship in Collaborative Neuroscience

Title: Beyond single cues: multimodal entrainment of the circadian clock

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Abstract: Circadian rhythms coordinate daily patterns of sleep, feeding, activity, and metabolism through the action of the suprachiasmatic nucleus (SCN), the central pacemaker of the mammalian brain. Although light is the dominant zeitgeber for SCN entrainment, nonphotic cues such as feeding and exercise also influence circadian timing. However, most circadian studies investigate these cues individually, which may not reflect the complex multisensory timing environment encountered under natural conditions.To address this gap, we developed LiFE, a multimodal entrainment paradigm integrating timed light exposure, feeding, and exercise to investigate how coordinated environmental signals shape circadian function. Circadian rhythmicity was assessed using PER:LUC bioluminescence recordings and LumiCycle-based analyses of rhythm amplitude and phase. The combined LiFE intervention produced stronger circadian outputs than single-cue paradigms. Specifically, LiFE significantly enhanced rhythm amplitude, while time-restricted exercise preferentially advanced circadian phase onset. These findings suggest that distinct environmental cues may differentially regulate specific features of the circadian clock, with multimodal input strengthening overall rhythm robustness while individual cues selectively tune clock timing. It supports a systems-level framework for circadian entrainment in which behavioral and environmental signals act cooperatively rather than independently. More broadly, the findings highlight multimodal chronotherapy as a potential nonpharmacological strategy for improving circadian alignment, sleep, and metabolic health.

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Title: Circadian gating of vagal signaling drives day-night differences in glucose-stimulated insulin secretion

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Abstract: Postprandial blood glucose regulation follows a daily rhythm. In nocturnal rodents, glucose tolerance peaks at the onset of the dark phase, coinciding with the peak in food intake. Here, we identify vagal sensory neurons in the nodose ganglia (NG) as key mediators of these circadian fluctuations in glucose tolerance. Using live calcium imaging (n=5/time) and Fos-TRAP labeling (n=7/group) in male mice, we found that glucose activates NG neurons and the dorsovagal complex more strongly during the dark than the light phase. Deleting the clock gene Bmal1 in the NG abolished day-night differences in glucose tolerance by selectively reducing dark-phase insulin secretion, suggesting that the local vagal clock is required for circadian glucose control (n=6/group). Ablation of vagal cocaine-and amphetamine-related transcript (CART) NG neurons (n=7/group) impaired circadian glucose tolerance and insulin secretion, whereas selective re-expression of CART in the NG of global CART knockout mice (n=6/group) rescued both, indicating that CART signaling in the NG was necessary and sufficient for circadian glucose tolerance. Finally, one week of a high-fat diet (n=6/group) abolished day-night differences in glucose tolerance and vagal signaling. Together, these findings establish CART+ vagal sensory neurons as a key peripheral component of the circadian regulation of glucose homeostasis. By fine-tuning their response to glucose at different times of day, vagal sensory neurons modulate insulin secretion according to the body's metabolic needs across the circadian cycle.

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Nanosymposium

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Presentation Number: NANO03.05

Topic: F.08. Respiratory Regulation

Support: R01HL174409
26POST1558653

Title: Role of melanocortin 4 receptor signaling in genioglossus muscle activity

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Abstract: Background: Obstructive sleep apnea (OSA) affects many people throughout the world and is a leading cause of cardiovascular morbidity and mortality. One of the major causes of OSA is loss of genioglossus (GG) muscle tone during sleep. Emergent pharmacotherapy has limitations and new drugs with a better potential to treat OSA are required. We have previously shown that melanocortin 4 receptor (MC4R) agonist setmelanotide (SET) improves breathing in diet induced obese (DIO) mice acting in the retrotrapezoid nucleus (RTN). **Objective:** We hypothesize that SET treats OSA by increasing GG muscle tone and that effects of SET on sleep and breathing can be localized to the MC4R on the RTN neurons. **Methods:** We transfected DIO MC4R-flox mice with AAV-Cre-recombinase (icre) into the RTN. DIO MC4R-flox and C57BL/6J mice were headmounted with EEG and GG electrodes. Sleep and hypercapnic ventilatory response (HCVR, 8% CO_2 challenge) studies were performed in the plethysmography chamber. **Results:** SET (1 mg/kg, i.p) significantly increased GG muscle activity during NREM sleep (SET: 0.86 ± 0.08 vs. Veh: 0.48 ± 0.04 a.u.; $p < 0.005$), REM sleep (SET: 0.38 ± 0.05 vs. Veh: 0.27 ± 0.04 a.u.; $p < 0.05$) and during HCVR (SET: 2.04 ± 0.25 vs. Veh: 1.25 ± 0.11 a.u.; $p < 0.05$). Experiments in MC4R-flox mice showed that MC4R knockdown in RTN abolished effects of SET on HCVR (control, SET: 0.29 ± 0.02 vs. Veh: 0.25 ± 0.03; $p < 0.05$; MC4R knockdown, SET: 0.17 ± 0.03 vs. Veh: 0.19 ± 0.04; $p > 0.05$). Furthermore, MC4R knockdown in RTN-MC4R neurons abolished SET- induced increase in GG activity. **Conclusion:** Our study suggests SET targets RTN-MC4R neurons to augment HCVR and that SET may treat OSA by improving GG muscle activity.

Disclosures: M. Islam: None. **M. Shin:** None. **N. Williams:** None. **D. Davaanyam:** None. **M. Alexis Ruiz:** None. **D.S. Mendelowitz:** None. **V. Polotsky:** None.

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Topic: F.08. Respiratory Regulation

Support: R01 HL126523
R01 HL151389

Title: Ventrolateral Medullary Astrocytes Engage C1 Neurons to Coordinate Arousal State Transitions and Sigh Generation

Authors: *L. M. OLIVEIRA[1], N. C. MIRANDA[1], L. LI[2], J. M. RAMIREZ[3];
[2]Anesthesiol. and Pain Med., [1]Seattle Children's Res. Inst., Seattle, WA; [3]Seattle Children's research Inst., Seattle, WA

Abstract: Here, we investigated whether astrocytes within the ventral respiratory column (VRC) interact with C1 neurons to regulate arousal and sigh generation. Our results reveal that a subset of Aldh1l1 cells in the VRC are activated prior to sigh generation and are recruited by hypoxia.

Using chemogenetic and optogenetic approaches in Aldh1l1-Cre mice, we found that activation of Aldh1l1-positive astrocytes in the VRC increased respiratory frequency, sigh occurrence, and the probability of arousal. Fiber photometry recordings revealed that astrocyte activation robustly increased calcium activity in C1 neurons. Simultaneous optogenetic stimulation of astrocytes and calcium imaging of C1 neurons further demonstrated rapid astrocyte-to-neuron signaling during both wakefulness and sleep, providing direct evidence of a functional astrocyte-C1 neuron circuit within the VLM. To determine the contribution of C1 neurons to astrocyte-mediated responses, we selectively depleted catecholaminergic neurons using bilateral 6-hydroxydopamine injections. Although astrocyte photostimulation continued to evoke sighs and arousal after C1 neuronal depletion, response latencies were significantly prolonged, indicating that C1 neurons facilitate the rapid initiation of these behaviors. Complementary experiments using the activity-dependent reporter CaMPARI confirmed that astrocyte photostimulation recruits neuronal populations within the VRC in vivo, further supporting functional astrocyte-to-neuron signaling in this region. Mechanistically, pharmacological blockade of P2Y1 receptors in the VRC abolished astrocyte-driven sigh generation, respiratory modulation, and arousal responses. Together, these findings reveal that astrocytes in the VLM actively regulate arousal and sigh generation through functional interactions with C1 neurons. These results establish neuron-glia communication within the VRC as a critical component of adaptive arousal responses and respiratory state regulation.

Disclosures: L.M. Oliveira: None. **N.C. Miranda:** None. **L. Li:** None. **J.M. Ramirez:** None.

Nanosymposium

NANO03: Respiratory Control

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Topic: F.08. Respiratory Regulation

Support: BBRF YI Grant 33224

Title: Mistimed eating disrupts rhythmicity though a subset of lateral hypothalamus neurons

Authors: E. N. DOHERTY[1], M. YOUNG[1], S. DHARAP[1], ***L. N. WOODIE**[2];
[1]Pharmacol. and Physiol., George Washington Univ., Washington, DC; [2]Pharmacol. and Physiol., George Washington Univ., Washington, VA

Abstract: Synchrony between the light-entrained suprachiasmatic nucleus and food-entrained circadian clocks is critical for maintaining homeostasis in the face of varying environmental cues, while desynchrony among tissues is highly detrimental to organismal health. Individuals that consistently eat at the “wrong” time of day, common within shift working professions, experience disruptions in sleep and are inordinately affected by chronic diseases (e.g., cardiovascular disease, obesity, mental health disorders). Therefore, we hypothesized that mistimed eating, without changes in light:dark cycle, negatively impacts behavioral rhythmicity

and that specific subpopulations of “mistimed eating-sensitive” (MES) neurons regulate this phenotype. To test this, we used male and female transient recombination in active populations (TRAP2) mice crossed to a tdTomato reporter (TRAP2xAi14) and exposed them to a mistimed or timed eating paradigm. We found that a single bout of mistimed eating decreased the daily variation in energy expenditure, respiratory exchange ratio, activity, and rest patterns for 12 hours while a single bout of timed eating did not have this effect. Furthermore, we identified a subpopulation of neurons in the lateral hypothalamus (LH) that were uniquely sensitive to mistimed eating. To examine the role of these neurons in the metabolic and behavioral phenotype induced by mistimed eating, we chronically activated them using a Cre-dependent sodium channel from bacteria (NaChBac) in male TRAP2 mice. Remarkably, constant activation of LH MES neurons prolonged the effects of mistimed eating and abolished daily variation in activity and rest patterns for 36 hours. In sum, a single bout of mistimed eating is sufficient to disrupt behavioral rhythmicity and MES neurons in the LH prolong this phenotype. To date, there are no viable treatments for the deleterious outcomes of mistimed eating. However, these findings indicate that MES neurons in the LH warrant further investigation as potential therapeutic targets to alleviate the burden of chrono-disruption.

Disclosures: E.N. Doherty: None. **M. Young:** None. **S. Dharap:** None. **L.N. Woodie:** None.

Nanosymposium

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Presentation Number: NANO03.08

Topic: F.08. Respiratory Regulation

Support: NIH Grant R01ES035118

Title: Food Type Dependent Relationship of Nigral Dopamine Loss and Pharyngeal Function in a Rat Model of Parkinson’s Disease

Authors: *C. J. PELLETIER[1], I. WOJTAS[1], V. SICA[2], F. GOULD[1];
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Abstract: Dysphagia, or pathological swallowing, is one of the most common clinical manifestations of Parkinson’s Disease (PD), with prevalence rates estimated as high as 80%. The shared aerodigestive anatomy of the laryngopharynx makes impaired pharyngeal bolus propulsion a threat to airway integrity. Consequently, chronic aspiration plagues PD patients, with aspiration pneumonia representing one of the leading causes of death. Unlike canonical Parkinsonian motor dysfunctions, which are largely the result of dopamine loss in the midbrain nigrostriatal circuitry, aspiration rates show inconsistent responses to dopamine agonists, suggesting the involvement of alternate mechanisms. Although aspiration is a consequence of dysphagia in the pharyngeal phase of swallowing, proper bolus management in the oral phase plays a critical role in safe pharyngeal transit. Solids require increased oral preparation, including

mastication prior to swallow initiation, exhibiting a heightened reliance on voluntary motor control in a consumable-specific manner. Despite being a consumable dependent behavior critical to survival, little work has investigated whether neurological impairment of swallowing in PD is similarly segregated across consumable consistency. Accordingly, the present study aimed to elucidate potential bolus consistency-dependent relationships between nigrostriatal dopaminergic capacity and pharyngeal transit time (PTT), given that prolonged PTT is a common dysphagic phenotype associated with heightened aspiration risk. To recapitulate systemic Parkinsonian progression, 6 rats received rotenone treatments (2.75 mg/kg) for 24 days while an additional 6 receiving vehicle injections (2.75 mg/kg) in the same timeline. On day 24, animals were recorded consuming barium coated Fruit Loops and water via video-fluoroscopy at 200 frames per second. Following recording, midbrain slices were collected for analysis of tyrosine hydroxylase (TH) expression in the substantia nigra. Using a linear model to analyze the relationship between TH+ cell counts and PTT revealed a significant negative correlation between the two metrics in rotenone treated animals exclusive to solid foods (Eating: correlation coefficient = -0.866, $p = 0.025$; Drinking: correlation coefficient = -0.155, $p = 0.7685$). The reported results provide evidence that swallowing behaviors critical for airway safety may utilize dopaminergic circuits in a consumable dependent manner, providing grounds for the variable response aspiration rates have demonstrated when exposed to pharmacological agents targeting the dopamine fueled motor pathway.

Disclosures: C.J. Pelletier: None. **I. Wojtas:** None. **V. Sica:** None. **F. Gould:** None.

Nanosymposium

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Topic: F.08. Respiratory Regulation

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VA I01BX006128-01A2

Title: Sensory-motor integration of carotid body chemosensory input across the brainstem respiratory network

Authors: G. KOLA[1], S. QIN[2], P. J. THOMAS[2], M. DUTSCHMANN[1], ***R. R. DHINGRA**[1]; [1]Dept. of Med., [2]Mathematics, Applied Mathemtics, and Statistics, Case Western Reserve Univ., Cleveland, OH

Abstract: A vital role of the brainstem respiratory network is to adapt the breathing pattern to changing environmental conditions and metabolic demands. Arterial hypoxia is transduced by peripheral carotid body (CB) chemoreceptors. CB stimulation evokes a stereotypical modulation of breathing, characterized by an acute phase wherein ventilation is augmented and a post-hypoxic phase in which ventilation is depressed below baseline. Dorsolateral pontine areas are

necessary for the expression of the physiologic respiratory motor pattern. Similarly, dorsolateral and ventrolateral pontine areas are necessary for the respiratory chemoreflex. Yet, despite the established contributions of pontine areas to the control of breathing, we do not understand the circuit level mechanisms by which pontine areas modulate medullary neuronal activities. Here, we inserted three high-density multi-electrode arrays (MEAs) into the dorsolateral pons and medullary ventrolateral respiratory column of an *in situ* arterially-perfused brainstem-spinal cord preparation of juvenile (P16-24) rats to test the hypothesis that CB stimulation modulates and reconfigures ponto-medullary respiratory network activity. Our approach enabled simultaneous monitoring of the ensemble activity of ca. 100 respiratory neurons across the ponto-medullary respiratory network. At baseline, medullary neurons largely had bursting firing patterns that were highly correlated with the motor pattern, whereas pontine neurons fired tonically. Consistent with previous reports, CB stimulation evoked an excitation of on-going medullary neuronal activities. Interestingly, CB stimulation also recruited silent medullary neurons into the network and silenced active respiratory neurons. Overall, medullary population activity simply encoded the respiratory motor pattern. In contrast, while pontine population activity was tonic at baseline, we observed pontine ensembles that either became transiently oscillatory during the acute phase, or that encoded an alarm signal that peaked during the post-hypoxic phase. Taken together, we conclude that medullary and pontine neuronal populations jointly encode the slow modulation of the respiratory motor pattern during the acute and post-hypoxic phases of the CB-evoked respiratory chemoreflex.

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Nanosymposium

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Presentation Number: NANO03.10

Topic: F.08. Respiratory Regulation

Support: 5F31HL172642

Title: Enhanced chemoreception contributes to breathing problems in hypertension

Authors: *M. A. JOLLY, Jr;
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Abstract: Hypertension is a major risk factor for cardiovascular disease, yet the underlying mechanisms are poorly understood. Disordered breathing is common in hypertension patients, with breathing problems often preceding the development of high blood pressure, suggesting a potential causal role. We hypothesized that altered respiratory control contributes to the development and maintenance of hypertension through an enhanced chemosensory drive. To test this, we assessed breathing patterns and chemoreflex function in spontaneously hypertensive rats

(SHR) and normotensive Wistar Kyoto (WKY) controls across key developmental timepoints using unrestrained whole-body plethysmography. At two weeks of age, SHRs exhibited increased variability in baseline respiratory rate, preceding the emergence of hypertension by several weeks. Both central and peripheral chemoreflex responses were augmented in SHR and progressively worsened with development. To investigate underlying mechanisms, we performed patch clamp electrophysiology and immunohistochemistry in the retrotrapezoid nucleus (RTN), a critical chemosensitive brainstem region. Baseline firing rates and CO_2-evoked responses of individual RTN neurons were comparable between strains, but electrophysiological sampling revealed more abundant chemosensitive neurons in SHRs. This was confirmed with immunohistochemical staining for Phox2b (a cell-type specific marker), revealing an increased population of chemosensitive neurons in SHRs. Taken together, these results show that SHRs exhibit an altered respiratory phenotype early in life, marked by enhanced chemoreflex sensitivity and increased breathing variability. This phenotype precedes the development of hypertension, correlates with its severity, and appears to arise from a population-level enhancement of chemosensitive RTN neurons rather than altered intrinsic pH-sensing mechanisms. These findings suggest pathological breathing is an early biomarker of cardiovascular dysfunction and support a model where an enhanced central chemoreflex contributes to the development of hypertension.

Disclosures: M.A. Jolly: None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

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Civilian Foundation of Tri-Service General Hospital TSGH-B-112021

Title: Large-Scale Brain Network Architecture of Multidimension Fatigue: A Transdiagnostic Neuroimaging Meta-Analysis

Authors: *Y.-T. LIN[1], C. HSU[1], Y. LIN[3], Y.-Z. LEE[1], Y.-C. SU[1], Y. CHEN[1], L.-H. CHANG[2], C.-P. LIN[4];
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Abstract: Background: Fatigue is a prevalent and clinically challenging symptom whose multidimensional nature and reliance on self-reported assessment complicate timely diagnosis and treatment. Although cortico-striato-thalamo-cortical (CSTC) circuitry has featured prominently in previous studies, fatigue-related activations extend across multiple large-scale brain networks. This unresolved network organization of multidimensional fatigue limits biologically informed classification and treatment.
Objective: We proposed a CSTC-centered fatigue framework that extends prior findings limited to specific fatigue dimensions toward a transdiagnostic, multidimensional model of fatigue. In this meta-analysis, we tested the hypothesis that CSTC circuitry constitutes a shared neural core across fatigue dimensions, whereas subtype-specific interactions between CSTC circuitry and large-scale brain networks differentiate fatigue subtypes.
Methods: We conducted a PRISMA-guided systematic search of PubMed, identifying 8,642 records, of which 60 studies met the inclusion criteria: 33 examined trait fatigue and 27 examined state fatigue. Studies were classified by temporality (state versus trait) and affected domain (mental versus physical), referring to the Penner .et al framework. Activation likelihood estimation (ALE) and meta-analytic connectivity modeling (MACM) were performed on the included experiments, comprising 1,418 participants and 957 activation foci. Large-scale network organization was characterized using the Network Correspondence Toolbox with reference to the Yeo 17-network and Cole-Anticevic 12-network atlases.
Results: Fatigue-related activation patterns across temporal and domain dimensions converged on CSTC circuitry, but differed in cortical entry points. Each fatigue subtype exhibited a distinct CSTC-network interaction profile, involving different combinations of dorsal attention, frontoparietal, salience, and somatomotor networks.
Conclusion: This study supports a CSTC-centered framework of fatigue, in which differential CSTC interaction patterns with large-scale brain networks distinguish fatigue subtypes. These findings on CSTC interaction patterns provide a neurobiological basis for moving clinical fatigue assessment beyond subjective symptom reports, enabling more objective classification, providing more biologically informed interventions, and preventing the progression to chronic fatigue syndrome.

Disclosures: Y. Lin: None. **C. Hsu:** None. **Y. Lin:** None. **Y. Lee:** None. **Y. Su:** None. **Y. Chen:** None. **L. Chang:** None. **C. Lin:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

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Presentation Number: NANO04.02

Topic: H.03. Motivation

Support: R61-MH121560

Title: Basal Forebrain-Striatal Hyperconnectivity Supports a Novel Arousal Model of Negative Symptoms in Schizophrenia

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Abstract: Negative symptoms are a strong predictor of functional impairment, as well as numerous other poor clinical outcomes, in schizophrenia (SZ). Unfortunately, pharmacological treatments for negative symptoms have been ineffective, and they remain one of the most critical unmet needs in psychiatry. Limited treatment progress results, in part, from difficulty identifying separable mechanistic treatment targets for the two higher-order dimensions of negative symptoms (Motivation and Pleasure: MAP; Diminished Expressivity: EXP). The current study evaluated specific hypotheses regarding pathway associations with each dimension in a sample of 40 outpatients with SZ who completed resting-state fMRI scans. We hypothesized that reduced functional connectivity between the ventral striatum and ventromedial prefrontal cortex (vMPFC) (a pathway critical for value-based decision-making) would be more strongly associated with MAP than EXP, whereas reduced connectivity between the ventral striatum and Broca's area (a pathway critical for motivation to produce spontaneous speech) would be more strongly associated with EXP than MAP. In addition to these pathways, the basal forebrain—an important relay hub within the brain's ascending arousal system—has broad connections with Broca's area, the ventral striatum, and the vMPFC. Therefore, it was hypothesized that reduced functional connectivity between the basal forebrain and these three regions would be associated with both MAP and EXP deficits, introducing the brain's arousal system as a novel neural mechanism underlying negative symptoms. After FDR corrections, MAP was significantly associated with basal forebrain-striatum connectivity ($r = .45$, $p = 0.03$), but not connectivity between the basal forebrain and Broca's area ($r = .13$, $p = 0.81$) or the basal forebrain and vMPFC ($r = .09$, $p = 0.81$). EXP was not significantly associated with connectivity between the basal forebrain and any of the regions (r's $< .18$, $p > 0.76$). Results did not support hypothesized associations between MAP and striatal-vMPFC connectivity ($r = .08$, $p = 0.91$) or EXP and striatal-Broca's area connectivity ($r = .22$, $p = 0.62$). Findings did not support hypotheses regarding specific functional pathways that would be associated with MAP vs. EXP. However, there was partial support for the novel "arousal" hypothesis; contrary to expectations of reduced connectivity, greater basal forebrain-striatal connectivity was associated with more severe MAP symptoms, potentially reflecting maladaptive hyper-coupling of arousal and salience systems in response to impaired motivational drive.

Disclosures: K. Rogge-Obando: None. **A. Dhima:** None. **A.R. Knippenberg:** None. **J.E. Luck:** None. **J. Ehm:** None. **C. Chang:** None. **L. Luther:** None. **L.H. Sweet:** None. **G.P. Strauss:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

Time: Saturday, November 14, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO04.03

Topic: H.03. Motivation

Support: Lighthouse Partnership for AI-guided Neuromodulation, Geneva, Switzerland

Title: Modulating striatal circuits to shape apathy-related motivated decision-making in aging

Authors: *M. DI PONZIO[1], S. LOSACCO[2], L. HO DAC[3], F. WINDEL[4], B. LUGLI[5], P. MACEIRA ELVIRA[6], P. VASSILIADIS[7], F. C. HUMMEL[8];
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Abstract: Effort-based decision-making (EBDM), the process of balancing the costs and benefits associated with an action, underlies motivated behaviour (Husain & Roiser, 2018) and is important over one's entire lifespan and critical for everyday life activities of older adults (Brand and Markowitsch, 2010). Apathy, characterized by impaired goal-directed behaviour, has been linked to alterations in effort discounting (Husain & Roiser, 2018) and has been shown to be highly prevalent among older adults (Van Delen et al., 2018). At the neural level, age-related alterations in striatal function, which is involved in integrating effort and reward information (Croxson et al., 2009), may contribute directly to reduced motivation in aging (Yan et al., 2023). For this reason, older adults represent a biologically and behaviorally meaningful population in which to examine the causal contribution of striatal circuits to EBDM. Overcoming the limitations of reaching deep brain structures due to a depth-focality trade-off traditional non-invasive brain stimulation, transcranial Temporal Interference Stimulation (tTIS) has emerged as an innovative tool to non-invasively stimulate deep brain regions (Wessel & Beanato et al., 2023; Vassiliadis et al., 2024; Vassiliadis & Beanato et al., 2026). Here, we combined striatal tTIS with an effort-based decision-making task in randomized, double-blind, cross-over design in healthy older adults. We quantified decision profiles and used hierarchical drift diffusion modeling to estimate latent decision parameters. In parallel, we recorded pupil size and facial expressions during task performance to derive additional physiological and implicit readouts of decision-related processes. This multimodal approach allows to address a central challenge of motivated behaviour, namely that it reflects latent processes that are only partially captured by self-reported measures and overt behavior (Husain, 2025; Zhao et al., 2025). We observed that facilitatory

tTIS affected multiple components of motivated behavior in older adults. Indeed, tTIS increased willingness to accept offers at low reward levels, modulated the evidence accumulation process and impacted a decision-threshold mechanism. Furthermore, tTIS increased motivational vigor during effort production. These results support the potential of a tTIS-based protocol as an intervention to target impairment in motivation and effort-based decision making to promote independence in old age.

Disclosures: M. Di Ponzio: None. **S. Losacco:** None. **L. Ho Dac:** None. **F. Windel:** None. **B. Lugli:** None. **P. Maceira Elvira:** None. **P. Vassiliadis:** None. **F.C. Hummel:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

Time: Saturday, November 14, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO04.04

Topic: H.03. Motivation

Support: R00MH127291

Title: Naturalistic nest-foraging reveals stress-sensitive changes in effort-based motivated behavior and frontostriatal activity

Authors: *Y. EL ZOGHBY[1], A. CSISZAR[1], A. BANGAD[1], M. JACKSON[1], E. TSAI[1], B. KISTUPATI[1], A. DINKLANG[1], K. LAKSHMINARASIMHAN[1], E. MEYERS[2], P. PAREKH[1]; [1]Neurosci., Univ. of Texas at Dallas, Richardson, TX; [2]Bioengineering, The Univ. of Texas at Dallas, Richardson, TX

Abstract: Apathy is a highly prevalent syndrome characterized by reduced willingness to exert effort in pursuit of rewards. It is strongly associated with stress and commonly observed in neuropsychiatric disorders such as depression; however, the underlying neural mechanisms remain poorly understood. Previous work showed that anterior cingulate cortex (ACC) to the nucleus accumbens (NAc) pathway encodes effort-scaled reward signals in a water-restricted T-maze task, and ACC-NAc activity is disrupted by chronic corticosterone. It remains unclear whether chronic social defeat stress (CSDS) alters effortful, naturalistic and ethologically-relevant foraging behavior, and whether ACC-NAc activity tracks these changes in a naturalistic setting. We therefore used an established effort-based foraging task to assess how CSDS influences motivated behavior and ACC-NAc neural dynamics.
We first validated task-sensitivity to acute dopaminergic modulation. Using a counterbalanced crossover design in a cohort of male C57BL/6J mice (n=15, 12-16 weeks old), haloperidol reduced the amount of nesting material shuttled under easy effort demands (paired t-test, p=0.0002). We then tested whether CSDS disrupts effortful behavior across effort demands. While previous work shows that CSDS reduces effortful responding in operant lever-press tasks, our preliminary data in naturalistic effortful assay suggest stress blunts effort sensitivity reflected

in amount of nesting material shuttled (two-way repeated-measures ANOVA: group-by-effort interaction, p=0.5631). To infer the internal state of mice, we used machine-learning approaches to quantify movement kinematics and fit hidden semi-Markov models to distinct behavioral motifs. We identified engaged and disengaged latent states, with engaged states showing higher foraging probability and shorter latencies. In a separate cohort of male mice (control n=7, defeat n=6), we recorded calcium activity within ACC-NAc pathway using in vivo fiber photometry. We found that foraging bouts are associated with a decrease in ACC-NAc activity at bout-onset and an increase in activity at bout-offset. Preliminary mixed-effects analyses of foraging bouts further showed that ACC-NAc activity tracked effort demand.
Ongoing work is assessing whether CSDS alters transitions between engaged and disengaged behavioral states, and whether onset and during-foraging signal features vary by stress condition. Together, these findings support naturalistic nest-foraging as a stress-sensitive assay of motivated behavior and suggest that ACC-NAc dynamics track the initiation and persistence of effortful motivated behavior.

Disclosures: Y. El Zoghby: None. **A. Csiszar:** None. **A. Bangad:** None. **M. Jackson:** None. **E. Tsai:** None. **B. Kistupati:** None. **A. Dinklang:** None. **K. Lakshminarasimhan:** None. **E. Meyers:** None. **P. Parekh:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

Time: Saturday, November 14, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO04.05

Topic: H.03. Motivation

Support: NIH DP1 MH140021

Title: A GDF15-sensing danger circuit drives amotivation during chemotherapy

Authors: *D. AHMADI[1,3], K. ZANG[2], X. ZHU[2], A. ARORA[2], T. SUNDARESAN VENKATESAN[2], M. GAIDICA[2], A. KEPECS[2];
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Abstract: Organisms rely on neural circuits that monitor internal danger to adaptively regulate behavior. However, in conditions of persistent somatic stress such as chemotherapy, these responses can become maladaptive, producing debilitating amotivation and fatigue that limit quality of life and treatment adherence. Here we identify a chemotherapy-responsive danger-sensing circuit that drives amotivation and fatigue. Systemic chemotherapy-induced cellular stress selectively elevates circulating GDF15, a danger cytokine detected by GFRAL-expressing neurons in the area postrema (ArP). These neurons engage parallel relays through the nucleus of the solitary tract (NTS) and the parabrachial nucleus (PBN) to converge on midbrain inhibitory

nodes, suppressing mesolimbic dopamine release and attenuating effort-based motivation. Direct optogenetic and chemogenetic activation of this circuit is sufficient to reproduce these dopaminergic and motivational deficits, and recombinant GDF15 phenocopies these effects. Conversely, silencing ArP GFRAL neurons or restoration of dopamine tone via chemogenetics or pharmacology rescues motivational drive following chemotherapy. Thus, a conserved GDF15-GFRAL danger circuit links somatic stress to reduced behavioral drive, revealing a neural mechanism through which internal injury suppresses motivation.

Disclosures: D. Ahmadi: None. **K. Zang:** None. **X. Zhu:** None. **A. Arora:** None. **T. Sundaresan Venkatesan:** None. **M. Gaidica:** None. **A. Kepecs:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

Time: Saturday, November 14, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO04.06

Topic: H.08. Drugs of Abuse and Addiction

Support: Virginia Commonwealth University School of Medicine

Title: The Impact of Chronic Neuropathic Pain on Nicotine Withdrawal and Intake in Mice

Authors: *A. PALAMAR, A. OROS, B. BUTTAR, M. DAMAJ;
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Abstract: Nicotine dependence is a major public health issue highlighted by the adverse effects of smoking and rising e-cigarette use. Individuals with chronic pain are disproportionately affected by nicotine dependence as those who report chronic pain have significantly higher rates of smoking and/or e-cigarette use than those that do not cite chronic pain. Despite this prevalence, the mechanisms underlying this comorbidity are not well understood. Here, we utilize a mouse model of chronic neuropathic pain to understand its influence on nicotine intake, withdrawal, and nicotinic receptors. To model for chronic neuropathic pain, the chemotherapy drug paclitaxel was administered every other day (i.p.) for a total of four injections (32 mg/kg cumulative dose) to female C57BL/6J mice. Nicotine withdrawal was assessed using implantation of nicotine- (24 mg/kg/day) or saline-containing osmotic minipumps. Upon removal, affective and somatic signs of withdrawal were collected. Withdrawal behaviors were recorded at short-term (7 days) and long-term (45 days) timepoints of chronic neuropathic pain progression. Nicotine intake was assessed using the two-bottle choice paradigm (2BC) and a novel apparatus for oronasal-restricted nicotine vaping self-administration. In a nicotine-naïve cohort, tissues from the medial habenula (MHb) and interpeduncular nucleus (IPN) were collected after paclitaxel injections at short- and long-term timepoints. Samples were isolated and used for qRT-PCR to assess mRNA expression levels of various nicotinic acetylcholine receptor (nAChR) subunits. Administration of paclitaxel worsened somatic signs of withdrawal,

anxiety-like behavior, and anhedonia-like behavior in a time-dependent manner. Paclitaxel treatment also increased nicotine intake in both the 2BC test and vaping self-administration and differentially affected nAChR subunit expression in the MHb and IPN. These findings provide preliminary assessment of chronic neuropathic pain on various aspects of nicotine dependence and its effects on specific brain regions and receptor systems that mediate nicotine dependence.

Disclosures: A. Palamar: None. **A. Oros:** None. **B. Buttar:** None. **M. Damaj:** None.

Nanosymposium

NANO04: Neural and Physiological Mechanisms of Motivation: Fatigue, Apathy, and Reward-Based Decision-Making

Location: WCC Rm 144

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Presentation Number: NANO04.07

Topic: H.03. Motivation

Support: NIH Grant K01DA051662
NIH Grant R01DA058955
Whitehall Foundation Research Grant

Title: A glucagon-like peptide-1 receptor (GLP-1R) agonist reduces risky choices during a rodent gambling task and alters neural signaling and dopamine in the nucleus accumbens

Authors: M. MCGROSKY[1], K. SABA[1], B. STICKLER[1], E. W. HERRING[1], M. HAFENBREIDEL[2], M. M. TORREGROSSA[2], *S. E. MORRISON[1];
[1]Neurosci., [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: In recent years, glucagon-like peptide-1 receptor (GLP-1R) agonists, including brands such as Ozempic and Wegovy, have exploded in popularity for the treatment of obesity. In addition to curbing food cravings, these medications have shown great promise, in both humans and animal models, for reducing the desire for drugs of abuse. Because the neural basis of gambling disorder (GD) is similar to that of substance use disorders, there is reason to believe GLP-1R agonists might be an effective treatment for GD; therefore, we hypothesized that GLP-1R agonists might reduce risky choices in a gambling environment. To test this hypothesis, we examined the effects of systemic administration of a short-acting GLP-1R agonist, exendin-4 (Ex-4), on risky decision-making in rats performing a rodent gambling task (rGT) with win cues. Indeed, we found that Ex-4 reduced the proportion of risky choices and increased the proportion of optimal choices in a dose-dependent manner. This effect was primarily driven by the subset of animals categorized as strong risk-takers.
Reward-related cues (e.g., flashing lights and sounds signaling a jackpot) can be a driver of risky choices in humans and animals, and the nucleus accumbens (NAc) is a key brain area that drives approach to reward cues. Therefore, we also assessed the effects of Ex-4 on neural activity and dopamine release in response to cues and rewards. We found that Ex-4 altered the event-related activity of a substantial portion of NAc neurons, often attenuating excitatory responses to both

cues and rewards. Interestingly, however, a subset of neurons with reward-evoked inhibitions "flipped" their response to reward-evoked excitation following Ex-4 administration. Surprisingly, dopamine release in response to cues and rewards, measured using a fluorescent dopamine indicator ($GRAB_{DA}$), was elevated in a dose-dependent manner following Ex-4. We speculate that GLP-1R agonists may reduce the influence of reward-associated cues over behavior by diminishing their incentive salience.

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Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.01

Topic: I.08. Learning and Memory

Support: NSF Award 2342812

Title: Timing the past, planning the future: Distinct neural correlates guide prospective and retrospective confidence in time estimates

Authors: T. OZTEL[1], *M. WIENER[2];
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Abstract: In order to act within the world, our sense of time must both be flexible and, critically, dependable. While much work has been conducted on how humans learn and adapt to different time intervals, far less is known regarding how metacognitively aware humans are of their own sense of time. Recent studies have shown that humans can accurately track both the magnitude and direction of their timing errors on a trial by trial basis, even in the absence of feedback, and can use this to rapidly improve performance. However, this improvement depends both on how well one has performed and how well one is likely to perform in the future. Whether these two forms of metacognition, prospective and retrospective, derive from the same brain circuitry, and whether these overlap with circuits for timing, is unknown. To address this gap, we had participants perform a temporal production task during fMRI where they were given a target duration and asked to produce it with a button press response. Before each production, they rated how well they expected to perform (prospective confidence); after each production, they rated how well they believed they had performed (retrospective confidence). Behaviorally, retrospective judgments were made significantly faster than prospective judgments, showed lower mean confidence with higher variance, and were only weakly correlated with each other, suggesting these judgments draw on different information sources. Critically, we observed a clear dissociation between confidence types—even after controlling for response time differences. Prospective confidence uniquely engaged superior prefrontal regions including pre-supplementary motor area (SMA) and anterior cingulate cortex (ACC), right inferior frontal

gyrus, and anterior right lateral prefrontal cortex (alPFC). In contrast, retrospective confidence was characterized by greater activity in inferior structures, including ventromedial prefrontal cortex (vmPFC), precuneus, right postcentral gyrus, and visual cortex, raising the possibility that retrospective processes depend on representational "replay" of sensory information. Finally, BOLD activity in right occipital and left postcentral regions during timing performance parametrically varied with subsequent retrospective confidence judgments. Overall, these results suggest that temporal metacognition is implemented by distinct systems depending on its temporal orientation: prospective judgments engage forward-model computations within action planning circuits, while retrospective judgments engage evaluative readout of sensory and motor traces from the just-completed action.

Disclosures: T. Oztel: None. **M. Wiener:** None.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.02

Topic: I.08. Learning and Memory

Support: NIH MH134000

Title: Frontopolar cortex integrates emotional evidence over temporally extended sequences: evidence from fMRI and TMS

Authors: *R. C. LAPATE[1], J. WANG[2], M. LI[2];
[1]UC Santa Barbara, Santa Barbara, CA; [2]Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: The capacity to respond to dynamic emotional events in a time- and context-sensitive manner is essential for adaptive behavior. Emotional events unfold over time, yet little is known about how emotional signals are integrated across temporally extended durations to guide action. The frontopolar cortex (FPC), the anterior-most region of lateral prefrontal cortex, carries abstract, temporally extended control signals (Desrochers et al., 2015; Badre & Nee, 2018), has privileged access to amygdala-originated projections compared to other LPFC regions (Folloni et al., 2019), and holds emotional-valence representations relevant to goal-directed behavior (Bramson et al., 2020; Lapate et al., 2022; Stasiak et al., 2026). However, whether FPC integrates temporally extended emotional information to guide context-appropriate action remains unknown. Here, we tested the representational and causal roles of FPC in emotional-evidence integration using fMRI (N=65) and TMS (N=41). Participants viewed 12-s emotional sequences comprising four emotional images (2 negative, 2 positive; presented for 2-4 s) and were asked to track the predominant valence of each sequence. After each sequence, a colored cue indicated the rule mapping between predominant valence and action goal, which was followed by action execution. FPC activation progressively ramped across the sequence, with stronger ramping than in mid-LPFC or PMd. Predominant valence was reliably decodable from

FPC, and trialwise FPC classifier evidence scaled with the final cumulative balance of positive versus negative duration in the sequence—an effect not observed in mid-LPFC or PMd. To establish causal inference, we applied a putatively inhibitory TMS protocol, continuous theta-burst stimulation (cTBS), to individualized FPC targets defined by each participant's peak predominant-valence decoding. FPC cTBS selectively impaired task accuracy relative to mid-LPFC and control stimulation. Collectively, these findings indicate that FPC function plays a causal role in tracking duration-weighted emotional information to guide context-appropriate action.

Disclosures: R.C. Lapate: None. **J. Wang:** None. **M. Li:** None.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

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Topic: I.08. Learning and Memory

Support: Italian Ministry of University and Research under the call PRIN2022, project ID: CCPJ3J

Title: How sensory load shapes the neural processing and perception of visual durations

Authors: *D. BUETI[1], F. I. BELLOTTI[2], M. ZANON[2];
[1]Neurosci., Intl. Sch. for Advanced Studies (SISSA), Trieste, Italy; [2]Neurosci., SISSA, Trieste, Italy

Abstract: The sensory content and temporal structure of stimuli have been shown to consistently bias duration perception. Temporal intervals filled with continuous sensory input ("filled intervals"), are often perceived as lasting longer than intervals marked only by their onset and offset ("empty intervals"). Despite this robust behavioral finding, it remains unclear whether filled and empty intervals rely on similar or distinct neural mechanisms and, more generally, how sensory format shapes the neural processing of millisecond time. To address this question, we asked twenty-one healthy participants to reproduce visual durations across different stimulus configurations while high-density scalp EEG was recorded. Behavioral results revealed differences in performance across stimulus configurations. Event-related potentials (ERPs) recorded at occipito-parietal and fronto-central electrodes between 0.1 and 0.4 s after duration offset were modulated in amplitude by both stimulus duration and format. These modulations scaled with the sensory load of the stimulus and its duration, suggesting a common underlying mechanism. A Representational Similarity Analysis (RSA) of the ERP data showed that perceived time was represented more strongly than physical time particularly at occipito-parietal electrodes, but only within the 0.2-0.3 s post-offset window, where stimulus format exerted a pronounced effect on the ERP signal. These findings highlight the role of sensory processing in

shaping duration perception and its neural coding, and reveal an early neural signature of perceived time in occipito-parietal electrodes.

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Nanosymposium

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Presentation Number: NANO05.04

Topic: I.08. Learning and Memory

Support: Whitehall Foundation
Chan Zuckerberg Initiative
Research Corporation for Science Advancement

Title: Intrinsic timing, not temporal prediction, underlies ramping dynamics in visual and parietal cortex, during passive behavior

Authors: *F. NAJAFI[1], Y. HUANG[2];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Wallace H. Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. / Emory Univ., Atlanta, GA

Abstract: Ramping neural activity is widely interpreted as a signature of predictive processing, but whether such signals truly reflect predictions or instead emerge from sensory mechanisms remains unclear. To address this question, we used two-photon calcium imaging across multiple cell types in visual and parietal cortex while awake mice passively received repeated audiovisual stimuli presented under distinct temporal structures. Neurons segregated into two broad response classes: stimulus-activated (ramp-down) and stimulus-inhibited (ramp-up) populations with diverse temporal kinetics. Multiple findings argued against a predictive interpretation: ramping activity was present in naïve animals, neural responses changed immediately after short/long interval transitions, and unexpected stimulus timings elicited nearly identical responses in predictable and irregular contexts. Population analyses further showed that ramping reflected relaxation from stimulus-evoked activity rather than anticipatory buildup. Heterogeneous kinetics generated a robust population code for elapsed time. Together, these findings show that neural ramps during passive stimulation arise from stimulus-evoked dynamics that intrinsically generate temporal signals, rather than from temporal predictive processing.

Disclosures: F. Najafi: None. **Y. Huang:** None.

Nanosymposium

NANO05: Time Across Systems and Species

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Presentation Number: NANO05.05

Topic: I.08. Learning and Memory

Support: ERC CHRONOLOGY, 101167367
European Commission H2020 Framework Program, 101017727

Title: Beyond the mental timeline: uncovering the multidimensional geometry of duration representation

Authors: *C. L. GRASSO[1], L. NALBORCZYK[2], V. VAN WASSENHOVE[3];
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Abstract: How does the brain represent duration? Durations are often assumed to be organized along a mental timeline: a single axis running from short to long intervals. We tested whether this one-dimensional account is sufficient to describe the psychological and neural geometry of duration. Thirty-three healthy adults completed two sessions using the same set of ten auditory durations, ranging from 400 to 2200 ms. First, they rated the perceived similarity of all duration pairs. Second, EEG was recorded while they detected rare duration oddballs in a continuous auditory stream. We converted behavioral judgments and EEG patterns into representational dissimilarity matrices and compared them with theoretical models of duration organization, including linear, logarithmic, power-law, and helical geometries. Behavioral similarity judgments revealed a coherent three-dimensional duration space. One dimension reflected monotonic magnitude, a second encoded distance from the geometric mean of the experienced range, and a third periodic component. A generalized helix captured this structure while preserving out-of-sample predictive performance under leave-one-duration-out cross-validation. Time-resolved EEG representational similarity analysis showed that duration geometry was assembled dynamically after stimulus offset. Around 150 ms, neural dissimilarities were best explained by a compressed logarithmic code and by task-relevant regularity relative to oddball anchors. Around 300 ms, EEG geometry became more strongly aligned with behavioral similarity structure and with a broader spring-like or helical organization. Finally, interindividual variation in the helix parameter was associated with resting alpha and beta power, suggesting that intrinsic oscillatory dynamics may constrain the geometry of subjective duration. These findings challenge the view that duration is represented only along a single mental timeline. Instead, they indicate that human duration representations are multidimensional, dynamic, and partly shaped by endogenous neural rhythms.

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Nanosymposium

NANO05: Time Across Systems and Species

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Presentation Number: NANO05.06

Topic: I.08. Learning and Memory

Support: DP2NS132108

Title: Population geometry of value-based decisions under conflict during temporal discounting

Authors: *Y. JUNG, D. OKADA, H. INAGAKI;
Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Decisions are often difficult because desirable outcomes come at a cost—for example, lower prices may require longer waits, whereas immediate availability may demand a premium. To choose between such conflicting alternatives, the brain must transform multiple, incommensurable decision attributes into a single action. How frontal cortical circuits implement this transformation remains unclear. Here, we combined large-scale Neuropixels recordings, population analyses, and causal perturbations in mice performing a temporal discounting task that required balancing reward magnitude against reward delay. Across frontal cortical regions, neural activity exhibited distinct representational geometries. Ventral prefrontal cortex (vPFC) encoded task variables within high-dimensional neural subspaces segregated by delay context. The geometry of these representations predicted individual differences in decision strategy across animals, suggesting that vPFC maintains context-specific information relevant for resolving decision conflict. In contrast, premotor and dorsal prefrontal regions organized activity along a low-dimensional choice axis that generalized across task conditions. The magnitude of this axis tracked action value and predicted upcoming choices across contexts, consistent with a common-currency representation for action selection. To test the causal contribution of these circuits, we transiently silenced frontal regions during decision formation. Silencing dorsal frontal regions disrupted choice behavior across both conflict and non-conflict conditions, indicating a general role in action selection. In contrast, vPFC silencing selectively impaired decisions involving reward-delay conflict while sparing simpler value comparisons. Under vPFC silencing, animals behaved as if delay information was ignored, adopting a context-independent decision strategy. Simultaneous recordings revealed that vPFC perturbation altered delay-dependent activity in dorsal frontal populations, linking contextual representations to downstream choice dynamics. Together, these findings suggest a circuit mechanism for resolving decision conflict in frontal cortex. vPFC maintains an expanded representation of decision variables that preserves contextual information and individual decision strategies, whereas dorsal frontal circuits transform this information into low-dimensional dynamics that drive action selection. These results provide a population-level framework for understanding how the brain converts multidimensional value information into discrete choices.

Disclosures: Y. Jung: None. **D. Okada:** None. **H. Inagaki:** None.

Nanosymposium

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Topic: I.08. Learning and Memory

Title: Electrophysiological signature of explicit and implicit timing across the adult lifespan

Authors: *G. MIONI;
Dept. of Gen. Psychology, Univ. of Padova (Italy), Padova, Italy

Abstract: Temporal processing can be engaged explicitly (conscious duration estimation) or implicitly (incidental timing driving motor preparation). A previous EEG study in young adults showed that both the N1/P2 and CNV components, as well as beta desynchronization, were larger during implicit than during explicit timing, suggesting a prominent role for temporal expectation and motor preparation. The present study extends this work by examining whether these electrophysiological signatures are preserved or altered in healthy ageing. Twenty-three older adults (age M = 70.55, range 62-87) completed a time bisection task (explicit timing) and a matched foreperiod task (implicit timing) with concurrent EEG. Data were compared with 28 young adults (age M = 23.3) from the previous study. Tasks were matched for sensory and response demands. ERP (N1/P2, CNV), time-frequency (beta ERD), and EEG-behaviour analyses were performed using cluster-based permutation tests and linear mixed-effects models. Results showed that, within the elderly group, N1/P2 was larger for implicit than explicit timing at the shortest interval (480 ms). Crucially, CNV amplitudes were significantly reduced in older compared to younger adults in both tasks, with the effect being more pronounced and widespread in the implicit task. Beta desynchronization was also diminished in older adults, specifically during implicit timing, with a fragmented temporal profile (early and late bursts) replacing the sustained modulation seen in young adults. EEG-behaviour analyses revealed that the relationship between N1/P2 amplitude and temporal sensitivity (JND) reversed with age: larger N1/P2 predicted lower JND in young adults but higher JND in older adults. These findings suggest that ageing selectively attenuates the neural mechanisms supporting temporal expectation and motor preparation, particularly under implicit timing demands, while partially sparing early attentional allocation. The age-dependent reversal of EEG-behaviour relationships further points to a reorganisation of the neural systems linking anticipatory brain activity to temporal precision.

Disclosures: G. Mioni: None.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.08

Topic: I.08. Learning and Memory

Support: Region Normandy Label Excellence
Fondation de France 00135006 WB- 2022-42339

Title: A multiscale investigation of aging effects on temporal processing networks

Authors: *T. T. HINAULT;
INSERM U1077, CAEN, France

Abstract: Advancing age is associated with changes in the perception of time and in the temporal structuring of memory. However, the brain mechanisms underlying the reported changes in various aspects of temporal processing (order and rhythm processing, duration processing, felt passage of time, mental time travel) remain poorly known. We hypothesize that a disruption in synchronized brain communications could be associated with changes in temporal processing with age and that it may be predictive of longitudinal trajectories in older individuals. As part of the TIMES project, volunteers are currently performing a series of tasks assessing temporal processing while undergoing simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI) recordings and PET dopaminergic imaging (FDOPA). The present study focuses on the analysis of functional MRI and EEG data acquired from forty healthy older adults (OA group; 60 - 85 years) and forty young adults (YA group; 20 - 35 years) while they performed a temporal generalisation task. Participants were presented with various durations and asked to judge whether each was the same as or different from a previously learned reference duration (1500 ms), followed by a neuropsychological assessment. Both YA and OA appeared to discriminate the reference duration, but OA were more likely to report “same” for durations shorter than the reference, with greater interindividual variability for the shortest duration. At the cerebral level, the YA>OA contrast revealed no significant difference in the amplitude of cerebral activation between the two groups. However, the OA>YA contrast revealed several clusters. The first cluster comprises frontal regions including right supplementary motor area (SMA) as well as right middle and superior frontal gyrus. The second cluster comprises temporal, insular and frontal regions, including right middle temporal gyrus, right insula, and right inferior frontal gyrus opercular and orbital part. The thirds cluster contains temporal regions including right middle and superior temporal gyrus. Analyses of EEG source activity in the regions identified by fMRI analyses showed differences between young and older adults in theta phase synchronization in frontal and parietal regions that were associated with behavioral performance. The application of multi-level modeling (EEG-fMRI) to the study of the dynamics of networks associated with temporal processing provides new insights into the evolution of the neural bases of temporal processing with age and the heterogeneity of cognitive trajectories in older individuals.

Disclosures: T.T. Hinault: None.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.09

Topic: I.08. Learning and Memory

Support: R01NS120987

Title: Prefrontal dopamine controls timing variability

Authors: *N. S. NARAYANAN;
Univ. of Iowa, Iowa City, IA

Abstract: Timing intervals require precision and accuracy. We use an interval timing paradigm that requires participants to indicate their estimate of an interval of several seconds with a motor response, and capture accuracy by measuring the central tendency of responses, and precision with coefficient of variation or standard deviation divided by the mean. Strikingly, in our study of 90 patients with Parkinson's disease (PD), we found increased timing variability that predicted PD-related cognitive deficits and executive dysfunction. We investigated the bases of these deficits in mouse models, in which lesioning ventral tegmental area (VTA) mesocortical but not nigrostriatal dopamine neurons increased temporal variability. Inhibiting VTA dopamine neurons recapitulated increased variability but also attenuated prefrontal timing mechanisms such as time-dependent ramping and 4 Hz rhythms. Further, the activity of VTA dopamine neurons as measured by GCaMP was strongly modulated at the start of temporal intervals, and trial start-related activity predicted temporal variability. Drift-diffusion modeling indicated these deficits could be captured by increased drift noise and predicted that precise model-guided stimulation had the potential to decrease noise and recover temporal precision. In line with this model, we found that stimulation of VTA dopamine neurons improved timing by decreasing temporal variability in both intact and dopamine-depleted animals. Our data establish a model of cognitive symptoms of human PD and provide insight into the neuronal control of temporal variability, which impacts a wide range of executive functions. Precision defines successful behavior, yet the brain mechanisms promoting precision are unclear; thus interventions increasing precision will inspire new therapies for PD and other diseases that degrade executive function.

Disclosures: N.S. Narayanan: None.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.10

Topic: I.08. Learning and Memory

Support: NIH grant UF-NS108177
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Title: Dopamine reward transients calibrate the propensity to move via next-trial updates to movement timing

Authors: *A. E. HAMILOS[1], I. C. WIJSMAN[2], Q. DING[1], P. ASSAWAPHADUNGSIT[2,1], Z. OZCAN[1], E. NORRI[1], K. REINHOLD[2,3], B. L. SABATINI[2,3], J. A. ASSAD[2,4];
[1]Whitehead Inst., Cambridge, MA; [2]Neurobio., Harvard Med. Sch., Boston, MA; [3]Howard Hughes Med. Inst., Chevy Chase, MD; [4]Inst. Italiano di Tecnologia, Genoa, Italy

Abstract: Dopamine neurons (DANs) are thought to play distinct roles in reinforcement learning and vigor, with ongoing debate about how/when endogenous DA can influence movement. Pharmacology also suggests DA can act as a tuning dial for movement [higher DA: increased vigor]. We thus suspected DA's dual roles in reward and movement might be linked via a process that uses reward information to tune the propensity to move to the situation—which we operationally defined as movement timing in a self-timed movement task [higher propensity: earlier timing]. On each trial of this task, mice received a cue and were rewarded if their next lick occurred during a hidden rewarded time window (e.g., 3-7s later), which had to be discovered through trial-and-error. Mice quantitatively adjusted their timing on the next trial in response to task feedback, which gradually led to improved task performance, suggestive of calibration. We used fiber photometry in sex-balanced cohorts to examine if outcome-related DA transients/dips (|DA|) were related to timing updates (GCaMP6f in DANs [SNc or VTA, n=4 mice] or DA indicators [e.g., dLight] in dorsolateral/ventrolateral striatum [DLS/VLS: n=17]). Surprisingly, rather than reinforce timing, |DA| amplitude predicted a proportional *change* in timing on the next trial—10-60s later (high |DA|: early-shift, low |DA|: late-shift). These effects were robust to behavioral non-stationarity, spurious movements and optical artifacts. Optogenetic DAN stimulation, calibrated to produce different amplitudes of VLS |DA| at the time of the trial outcome, showed that single |DA| exposures caused proportional next-trial timing updates (n=4 ChR2 mice); No Opsin control stimulation (n=4) did not affect timing. DA's updates accumulated across trials to explain goal-directed shifts in timing in response to a variety of different situations—changing reward windows, reward content, and satiety status. DA's timing updates generalized beyond timing paradigms to an unrelated cued-reaching task, where timing had no bearing on reward (n=8 mice). The rapid onset of these effects is difficult to reconcile with gradual synaptic plasticity, suggestive of faster mechanisms, such as neuronal excitability. Our findings shed light on how reward and disorders like Parkinson's disease may lead to changes in vigor.

Disclosures: A.E. Hamilos: None. **I.C. Wijsman:** None. **Q. Ding:** None. **P. Assawaphadungsit:** None. **Z. Ozcan:** None. **E. Norri:** None. **K. Reinhold:** None. **B.L. Sabatini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OptogeniX. **J.A. Assad:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OptogeniX.

Nanosymposium

NANO05: Time Across Systems and Species

Location: WCC Rm 143

Time: Saturday, November 14, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO05.11

Topic: I.08. Learning and Memory

Support: NWO Vidi
NWO DBI2
Radboud University

Title: Temporal control of movements in cortico-cerebellar circuits

Authors: *D. NARAIN;
Donders Institute, Radboud Univ., Nijmegen, Netherlands

Abstract: Behavior depends on the ability to use contextual cues to predict not only which actions are appropriate, but when they should occur. Across milliseconds to seconds, organisms learn temporal contingencies linking sensory context, action windows, and expected outcomes, and flexibly adjust movement timing as these contingencies change. One proposed mechanism for this flexibility is temporal scaling, in which neural population trajectories stretch or compress to generate actions over different durations. Recent work suggests that cerebellar-thalamic circuits may provide timing-related contextual inputs that shape cortical dynamics and control movement timing.To investigate this possibility, mice performed a context-dependent timing task in which a dark or light tunnel signaled different expected intervals for lever pulling. Failure to respond within the context-appropriate time window triggered a periocular airpuff, allowing animals to learn both action timing and aversive temporal contingencies. Mice acquired context-dependent lever-press timing and expressed well-timed conditioned eyeblink responses on correct trials, indicating learning of the task's temporal structure. Extracellular recordings from cerebellar lobule IV/V and the Simplex lobule revealed context-dependent activity in Purkinje cells and other cerebellar cortical neurons that tracked behavioral timing.To interpret how cerebellar output could influence temporally organized behavior, we combined recurrent neural network models of cortical population dynamics with circuit-level computational models of cerebellar-thalamo-cortical interactions. These models predict that contextual timing cues establish distinct initial conditions for cortical trajectories, enabling different movement latencies through temporal scaling, and that reducing cerebellar-driven thalamic input accelerates behavioral timing. Consistent with these predictions, optogenetic attenuation of cerebellar output produced faster lever-press responses. Together, these results suggest that cerebellar signals encode learned temporal contingencies and provide contextual control over cortical dynamics that determine when movements are expressed.

Disclosures: D. Narain: None.

Nanosymposium

NANO05: Time Across Systems and Species

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Presentation Number: NANO05.12

Topic: I.08. Learning and Memory

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Canada Foundation for Innovation – John Evans Leaders Fund
Garry Hurvitz Centre for Brain and Mental Health Catalyst grant

Title: Time cells in mouse and human hippocampus link working memory and temporal perception

Authors: *J. TAXIDIS[1,2];
[1]Neurosciences and Mental Hlth., The Hosp. For Sick Children, Toronto, ON, Canada; [2]Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Working memory (WM) and time perception are tightly interdependent cognitive processes. WM performance is shaped by implicit timing, and timing behaviour often requires maintaining and updating information across delays. However, whether a shared neurophysiological mechanism underlies the integration of memory and timing in the brain is still unclear. A candidate mechanism for integrating memory and time is the sequential activation of hippocampal time cells. In rodents, after presentation of a sensory cue, populations of pyramidal cells fire in temporally ordered sequences throughout the subsequent delay interval. Each neuron activates at a specific moment, collectively encoding both the identity of the preceding cue (WM maintenance) and the time elapsed since its presentation. I will present our work which combines longitudinal two-photon calcium imaging and one-photon voltage imaging in CA1 of mice performing a WM task. We identified cue-specific time-cell sequences tiling the delay period (Taxidis et al. *Neuron* 2020), regulated by inhibitory interplay (Taxidis et al. *Nature Neuroscience* 2025). We also found that these sequences, together with WM performance, are shaped by the expected delay duration (Dorian et al. *Cell Reports* 2025). Beyond rodents, I will also present our recent evidence that time cells exist in the human brain as well, and that those found in the hippocampus are linked to successful WM retention (Xiao et al. *bioRxiv* 2026). Finally, whether time cells support temporal perception itself is unknown. Using longitudinal two-photon calcium imaging in mouse CA1 during behavioral paradigms requiring interval timing, we have been examining how hippocampal time cell sequences emerge and evolve as animals learn to estimate time, as well as how these sequences are dysregulated in the Df(16)A mouse model of schizophrenia, a condition heavily associated with impairments in both time perception and WM. I will show pilot data indicating impaired timing in Df(16)A mice together with aberrant time cell sequences. Together, this work establishes hippocampal time-cell sequences as a common neural substrate for WM and temporal perception across rodents and humans and provides a platform to link timing deficits to hippocampal circuit dysfunction.

Disclosures: J. Taxidis: None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.01

Topic: A.02. Stem Cells and Reprogramming

Support: RS-2024-00440778
RS-2024-00332454

Title: Deep Learning-Guided Holotomography Reveals Early Structural Remodelling During Pluripotency Exit

Authors: *H. PARK[1], K.-J. YOON[2];
[1]Korea Advanced Inst. of Sci. and Technol., Yuseong-gu, Korea, Republic of; [2]Biol. Sci., KAIST, Daejeon, Korea, Republic of

Abstract: Real-time assessment of human pluripotent stem cell (hPSC) quality is critical for reproducibility and safety in regenerative medicine, yet current methods are invasive, labor-intensive, or highly operator-dependent. We present DeepHOPE (Deep-learning-guided Holotomography for Pluripotency Evaluation), a non-invasive, automatizable, and statistics-driven platform that integrates three-dimensional (3D) refractive index imaging with deep learning to assess pluripotency. DeepHOPE performs robustly across diverse contexts, including germ-layer differentiation, retinoic acid-induced differentiation, and mid-reprogramming cultures, enabling streamlined cell production workflows and improving the efficiency of midbrain dopaminergic neuron differentiation through informed colony selection. Mechanistically, DeepHOPE detects minute colony-scale topological changes that precede molecular loss of pluripotency. These early changes are associated with rapid F-actin remodeling, including apical-to-basal redistribution during early differentiation. Consistent with a functional role for cytoskeletal regulation in state transitions, sustained reduction of actomyosin tension decreases pluripotency, identifying cytoskeletal dynamics as an upstream determinant of early pluripotency exit.

Disclosures: H. Park: None. **K. Yoon:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.02

Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant PA-25-301

Title: A novel computational pipeline for analysis of hiPSC morphology to predict brain organoid differentiation potential

Authors: *G. D. VITELLI[1], G. BERMAN[2], A. KING[1], F. BIREY[1];
[2]Biol., [1]Emory Univ., Atlanta, GA

Abstract: Machine-learning (ML) based feature extraction algorithms have been utilized for their ability to classify and interpret how biological structures such as cell morphology predict function in an unbiased manner. Here, we apply this paradigm to investigate how colony morphologies of human induced Pluripotent Stem Cells (hiPSCs) can be predictive of developmental trajectories. hiPSCs and hiPSC-derived 3D brain organoids have emerged as novel technologies that enabled investigators to uniquely gain access to aspects of human neurodevelopment in a dish. However, one of the largest roadblocks to date has been variability in organoid differentiation outcomes, which has significantly hampered the system's potential as robust models of brain development and disease. Whether hiPSC morphology could be a robust predictor of organoid differentiation outcomes and serve as a predictor of its variability is unknown. To address this issue, we utilize computational approaches to effectively and unbiasedly resolve hiPSC growth features and detect relevant morphological cell classes. We hypothesize that this approach will reveal distinct morphological classes and the relative enrichment of these classes will be predictive to organoid differentiation potential. Here, we find that computationally extracted morphological features predict organoid fate-modifying hiPSC cell culture conditions. We previously found that differential culture conditions of hiPSCs can determine the regional fate of organoids grown from different hiPSC lines. Organoids express increased cortical markers when cultured in vitronectin/E8 and increased spinal markers when cultured in Cultrex/mTeSR. We imaged and analyzed hiPSC colonies from hiPSC lines grown in the same culture condition using the CellAssist system, which enables longitudional tracking and automated extraction of up to 20 different physical features from the same wells over time, and found that lines display different 2D and 3D morphological characteristics in different culture conditions, with Vitronectin/E8 promoting flatter, more consistent colonies when compared to Cultrex/mTeSR. A random forest ML model trained on top 50 most meaningful well-level features achieved robust prediction of culture condition. In the same lines, we also find colony morphology dynamically adapting over time in culture, as colonies become flatter and more circular over time. *These results indicate that hiPSC morphological features can predict organoid fate-modifying hiPSC cell culture conditions.*

Disclosures: G.D. Vitelli: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Thrive Bioscience Inc. **G. Berman:** None. **A. King:** None. **F. Birey:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.03

Topic: A.02. Stem Cells and Reprogramming

Support: NCATS Intramural

Title: Small Molecule Modulation of Lineage Bifurcation Between Cortico-Thalamic and Hypothalamic Neuronal Fates from Human Pluripotent Stem Cells

Authors: *F. S. DALY[1], Q. CHEN[1], S. RYU[1], C. MCKEE[1], C. SEN[2], P. ORMANOGLU[2], C. A. TRISTAN[1], V. M. JOVANOVIC[1];
[1]Stem Cell Translation Lab., [2]Natl. Ctr. for Advancing Translational Sciences, Natl. Inst. of Hlth., Rockville, MD

Abstract: The regional specification of neurons during early forebrain development is governed by tightly regulated signaling gradients along the dorsal-ventral and anterior-posterior axes. Small molecule-based differentiation protocols leverage these pathways to direct human pluripotent stem cells (hPSCs) toward defined neuronal identities, including ventral, hypothalamic lineages. However, the extent to which graded signaling inputs govern lineage bifurcation between distinct regional fates remains incompletely understood. Here, we investigate how modulation of a developmental signaling pathway influences lineage bifurcation during hPSC neural patterning. Using an established hypothalamic differentiation protocol, pathway activity was varied across a gradient of small molecule concentrations to assess its role in specifying neuronal identity. Cells were analyzed using western blot, immunofluorescence, and mRNA-sequencing to evaluate the balance between hypothalamic and cortico-thalamic neuronal markers. Immunostaining of differentiated neuronal cultures revealed a shift in regional identity, with higher pathway activation conditions favoring hypothalamic marker expression, while reduced activation promoted FOXP2+TBR1+TLE4+ cortico-thalamic and VGLUT1+ glutamatergic neuronal identities. RNA-sequencing further supported altered regional specification across conditions. While developmental signaling pathways are well known regulators of dorsal-ventral patterning, it’s leveraged here to specify two distinct neuronal subtypes. These results suggest that graded pathway activity functions as a dose-dependent regulator of neuronal fate specification and that modulation of a single signaling pathway is sufficient to drive lineage bifurcation between hypothalamic and cortico-thalamic identities. This finding highlights the sensitivity of early neural patterning to morphogen gradients and establishes a simplified, scalable framework for bifurcation between dorsal and ventral forebrain neuronal fate commitment.

Disclosures: F.S. Daly: None. **Q. Chen:** None. **S. Ryu:** None. **C. McKee:** None. **C. Sen:** None. **P. Ormanoglu:** None. **C.A. Tristan:** None. **V.M. Jovanovic:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.04

Topic: A.02. Stem Cells and Reprogramming

Title: Decomposition of technical and biological signals in KOLF2.1J derived scRNA-seq data

Authors: *P. GAUR[1], W. F. FLYNN[2], M. L. SUTHERLAND[4], E.-M. SURMANN[3], V. MENON[5], M. R. COOKSON[6];
[1]Columbia Univ. Dept. of Neurosci., New York, NY; [2]Single Cell Biol., The Jackson Lab., Farmington, CT; [3]The Jackson Lab., Chicago, IL; [4]Biohub, Chan Zuckerberg Initiative, Redwood City, CA; [5]Neurol., Columbia Univ., New York, NY; [6]Lab. Neurogenetics, Natl. Inst. Aging, NIH, Bethesda, MD

Abstract: Decomposition of technical and biological signals in KOLF2.1J derived scRNA-seq data Pallavi Gaur[1] 1, Eva-Maria Surmann[2], Vilas Menon[1], Mark R. Cookson[3]1. Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, NY, USA.3. Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, 20892, USAInduced pluripotent stem cells (iPSCs) have enabled powerful in vitro models of human biology, but genetic variability across donor lines adds to observed variance in experimental design. A standardized iPSC reference line KOLF2.1J has been proposed to address this challenge and improve cross-study comparability. Here, KOLF2.1J was differentiated into three major human brain cell types (neurons, microglia, and astrocytes) across 14 laboratories using pre-established protocols. We investigated sources of variation in the differentiation of KOLF2.1J by analyzing 629022 single cell RNA profiles generated from a total of 24 experiments that includes 6 protocols to differentiate astrocytes, 4 protocols to generate microglia and 2 for neurons. We incorporated factor analysis to investigate the biological and technical structure within the scRNA-seq datasets. After removal of genes that were associated with higher variance components, our analysis revealed biologically meaningful structure in scRNA-seq data specific to the three prominent cell types harvested. We identified factors associated with distinct biological processes, including proliferative states and both activated and homeostatic microglial programs. Some factors captured major axes of cellular segregation among neurons, astrocytes, and microglia, reflecting underlying biological programs driven by their factor-specific gene contributions. In addition, we observed a subset of factors that appeared to be protocol-specific, highlighting how choices in differentiation protocol may influence gene expression. In addition, we compare these KOLF2.1J differentiated cells to primary human brain post-mortem single-cell reference datasets from ROSMAP cohort to evaluate transcriptional similarity and assess how closely they recapitulate in vivo cellular states. Overall, these analyses support the idea that selection of reference lines can allow for strong integration of data across laboratories, improving reproducibility and stable interpretation of gene expression signatures.

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Nanosymposium

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Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.05

Topic: A.02. Stem Cells and Reprogramming

Support: Minnesota Partnership for Biotechnology
the Mayo Clinic Center for Multiple Sclerosis and Autoimmune Neurology
Mayo Clinic Edmonds Neuroregeneration Fellowship

Title: NEUROG3 drives glutamatergic differentiation and sustained functional maturation of human iPSC-derived neurons

Authors: *K. AWASTHI[1], P. STREGE[2], A. BEYDER[1], C. L. HOWE[3];
[2]Physiol. and Biomed. Engin., [3]Neurol., [1]Mayo Clin., Rochester, MN

Abstract: Forced expression of proneural transcription factors enables rapid neuronal differentiation from human pluripotent stem cell-derived neural stem cells, but the durability and maturity of induced neuronal states remain variable. Here, we evaluated NEUROG3 as an alternative to the commonly used NEUROG2 (alias NGN2) for neuronal induction in human iPSC-derived neural stem cells. Under matched differentiation conditions, NEUROG3 efficiently generated neurons expressing mature neuronal and excitatory glutamatergic markers, with greater neurite arborization and network complexity than NEUROG2-transduced cells. Functional analyses showed earlier and more robust spontaneous activity in NEUROG3-transduced cells, as assessed by calcium imaging and whole-cell patch-clamp recordings, with stronger spontaneous and evoked firing properties, consistent with enhanced electrophysiological maturation. Multi-omic profiling demonstrated that NEUROG3 shares an initial proneural program with NEUROG2 but diverges thereafter: ATAC-seq identified a distinct NEUROG3 chromatin landscape enriched for homeodomain transcription factor motifs at neuronal and synaptic loci, while bulk and single-cell RNA-seq showed sustained enrichment of excitatory neuronal and synaptic maturation programs and reduced progenitor/glial signatures over time. Digital footprinting further suggested that NEUROG3 promotes maturation by expanding a homeodomain regulatory network while also deepening the suppression of progenitor- and gliogenic-associated transcription factor programs. NEUROG3-transduced cells remained predominantly glutamatergic, with a minor GABAergic component, potentially advantageous for neural circuit modeling. Together, these findings identify NEUROG3 as a potent driver of sustained neuronal maturation and a promising programming factor for generating functionally mature human excitatory neurons from neural stem cells.

Disclosures: K. Awasthi: None. **P. Strege:** None. **A. Beyder:** None. **C.L. Howe:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.06

Topic: A.02. Stem Cells and Reprogramming

Support: Research to Prevent Blindness
UM1 TR004399
the Intramural Research Program of the National Eye Institute, NIH (SPB)

Title: Multimodal Neuroprotection by H105A peptide in a Human Retinal Organoid Model of AMD-Associated Photoreceptor Degeneration

Authors: *S. PARWEEN[1], N. YANG[1], S. BECERRA[2], N. VERGARA[1];
[1]Ophthalmology, Univ. of Colorado, Sch. of Med., Aurora, CO; [2]Section of Protein Structure and Function, Lab. of Retinal Cell and Mol. Biol., Natl. Eye Institute, Natl. Inst. of Hlth., Bethesda, MD

Abstract: Dry age-related macular degeneration (AMD) is a leading cause of irreversible vision loss,characterized by progressive degeneration of the retinal pigment epithelium and photoreceptors.Current therapies provide limited protection against photoreceptor loss. Human iPSC-derivedretinal organoids recapitulate key features of the human retina and provide a translationalplatform to investigate therapeutic interventions for photoreceptor degeneration. The H105Apeptide, a bioactive fragment of pigment epithelium-derived factor (PEDF), has demonstratedneuroprotective activity in retinal degeneration models. This study aimed to unravel themechanisms underlying its protective effect on photoreceptors and evaluate its potential as anovel treatment for dry AMD. To model AMD-associated photoreceptor degeneration, humanretinal organoids were exposed to cigarette smoke extract (CSE) and simultaneously treated withH105A or control peptides. Phospholipase activity was assessed in response to H105A in thismodel. Cell death was assessed using live organoid assays with PSVue-794 and SytoxGreendyes. Photoreceptor survival was determined by immunofluorescence staining of rod or conephotoreceptors together with cleaved caspases. Apoptotic signaling was evaluated by westernblotting for BAX, BCL2, and caspase-related markers. Ferroptosis-associated changes wereassessed using live organoid assays that measured intracellular iron accumulation and lipidperoxidation. Cell lysates were used to measure glutathione redox balance. Calcium-mediatedcell death regulators were examined by quantifying calpastatin, cathepsin D, and calpain activity.Our results showed that H105A treatment effectively reduced photoreceptor degeneration inhuman retinal organoids exposed to CSE. Mechanistically, H105A suppressed the intrinsicapoptotic pathway and reduced ferroptosis by decreasing iron accumulation, limiting lipidperoxidation, and maintaining redox balance. The ability of H105A to target multiple mechanisms of photoreceptor degeneration in a human disease-relevant retinal organoid model highlights its therapeutic potential for dry AMD and other retinal neurodegenerative disorders.

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Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.07

Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant R01 MH130441
Autism Science Foundation Grant 24-005

Title: Modeling cortical surface area hyperexpansion in autism using induced pluripotent stem cell (iPSC) derived organoids

Authors: *R. SINGLA[1,2], J. PARK[2], K. PIERCE[2], J. VALONE[2], J. BACHMAN RODRIGUEZ[2], A. BELTRAN LOPEZ[2], J. WOLTER[3], M. R. GLASS[4], R. BATRA[5], A. BELTRAN[2], N. MARRUS[6], S. DAGER[7], A. ESTES[7], N. ALVAREZ[8], R. T. SCHULTZ[9], C. DUGO[8], Y. KIM[2], M. HARFOUCHE[8], M. A. STYNER[2], H. HAZLETT[2], J. GIRAULT[2], M. D. SHEN[2], J. PIVEN[2], J. L. STEIN[2];
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Abstract: Early cortical surface area hyperexpansion from 6-12 months has been observed in infants who later develop autism within the Infant Brain Imaging Study (IBIS), the largest longitudinal study of infants (>250 participants) at high familial likelihood for autism. While this research has provided key insights into early brain development, the cellular and molecular mechanisms driving this overgrowth remain unknown. To address this, our lab generated iPSCs from 115 IBIS participants: high-likelihood individuals who developed ASD (HL+), high-likelihood who did not (HL-), and low-likelihood who did not (LL-): all with longitudinal neuroimaging (6-24 months), behavioral assessments, and genotyping. We hypothesize ASD cortical overgrowth is driven by increased proliferative neural progenitor cells making symmetric cell fate decisions prenatally. To test this, we generated human cortical organoids (hCOs) differentiated to 84 days, completing differentiation for 108/115 participants. Organoid cross-sectional area correlated with in vivo cortical surface area growth in the same individual across multiple timepoints: for example, organoid growth from day 18 to 35 correlated with MRI-measured growth from 12 to 24 months (Pearson, $r=0.502$, $p< 0.05$, FDR corrected). Male derived organoids were significantly larger than female derived organoids from D18 ($p<0.05$) to D84 ($p<0.001$), mirroring known in vivo sex differences in cortical surface area, validating fidelity of cortical organoids as a model of inter-individual variation. Single cell RNA sequencing across 108 participants at day 14 and 84 yielded 1.5M high quality cells: the largest iPSC derived organoid scRNA seq dataset in an autism cohort. Annotations revealed expected cortical progenitor and neuronal subtypes, with proportions shifting from progenitor dominated at day 14 to neuron rich at day 84. Cell type composition was more correlated within replicates of the same participant than across participants ($p=0.005$ at D14; $p<0.001$ at D84), suggesting genetic background primarily drives cell type proportions. For lineage tracing, we introduced

STICR (single cell RNA seq compatible lineage tracer with ~35 million unique barcodes) into hCOs from 31 donors. Across these experiments, 323K cells were sequenced, including 120K barcode positive cells, enabling tests of donor specific clonal expansion and radial unit organization. By combining organoid models, single cell RNA sequencing, lineage tracing, and clinical data, we aim to better understand ASD related brain development mechanisms in a deeply phenotyped iPSC population.

Disclosures: R. Singla: None. **J. Park:** None. **K. Pierce:** None. **J. Valone:** None. **J. Bachman Rodriguez:** None. **A. Beltran Lopez:** None. **J. Wolter:** None. **M.R. Glass:** None. **R. Batra:** None. **A. Beltran:** None. **N. Marrus:** None. **S. Dager:** None. **A. Estes:** None. **N. Alvarez:** None. **R.T. Schultz:** None. **C. Dugo:** None. **Y. Kim:** None. **M. Harfouche:** None. **M.A. Styner:** None. **H. Hazlett:** None. **J. Girault:** None. **M.D. Shen:** None. **J. Piven:** None. **J.L. Stein:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.08

Topic: A.02. Stem Cells and Reprogramming

Title: Isogenic hIPSC neurovascular unit on-a-chip for modeling blood-brain barrier transport and neuroinflammation

Authors: A. DEY, E. GREGUSKE, *R. S. DAUGHTERS;
Emulate Inc, Boston, MA

Abstract: Current in-vitro models for assessment of blood-brain barrier (BBB) transport do not integrate multiple brain cell types within a microfluidic system. Existing in-vitro models are primarily limited to Transwell co-cultures or simple organoids which lack functional complexity and fluid shear stress, resulting in models with limited translational relevance. Thus, we developed an iPSC isogenic, human-relevant Organ-Chip model to recapitulate the cellular diversity and functional interactions of the neurovascular unit (NVU) and the BBB. The model integrates five hiPSC-derived cell types of the NVU, within a perfused microenvironment that supports physiological barrier formation and cellular communication. The Organ-Chip is fabricated from minimally absorbing plastic and is composed of parallel microchannels separated by a porous, cell culture-treated membrane. Glia, neurons and pericytes are seeded into the parenchymal channel, and BMECs in the vascular channel. After cell seeding and stabilization, cells experience flow at a rate of 20 µL/h for 4 days. Morphology is monitored daily to assess cell health. Apparent permeability (P_{app}) is calculated to evaluate barrier integrity using fluorescent tracers (3kDa dextran and 0.5 Lucifer yellow CH). Effluent media is collected periodically for cytokine analysis, using exogenous IL-1β as a positive control. At the conclusion of the experiment, cells are fixed for immunofluorescence (IF) staining. IF verified the proper expression and localization of key biomarkers: MAP2 (neurons), GFAP (astrocytes), NG2

(pericytes), and Iba1 (microglia). IF and qPCR verified that BMECs in the vascular channel express key BBB associated markers (ZO1, GLUT1, P-gp, TfR1) and do not express epithelial markers (CLDN6, EPCAM1, TRPV6). Brightfield images also confirm brain cells exhibit characteristic morphologies including formation of integrated multicellular clusters and fibrous astrocyte processes with extensive projection networking. Furthermore, P_{app} values below 2×10^{-6} cm/s indicate a tight physiological barrier, ideal for drug discovery and BBB transport studies. Finally, measured cytokine levels are low, consistently under 200 pg/mL, indicating that the glia are maintaining a steady resting state. Upon stimulation, cytokine levels spiked over a 10-fold increase consistent with neuroinflammation, ensuring cells retain their functional capabilities. Thus, we establish a complex resting state isogenic NVU model, consisting of multiple brain cell types on a microfluidic device that minimizes drug absorption poised for drug discovery and neuroinflammatory applications utilizing small molecules.

Disclosures: A. Dey: A. Employment/Salary (full or part-time):; Emulate. **E. Greguske:** A. Employment/Salary (full or part-time):; Emulate Inc. **R.S. Daughters:** A. Employment/Salary (full or part-time):; Emulate Inc..

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.09

Topic: A.07. Development of Neural Systems

Support: NIH TL1 Grant
VA Merit Grant

Title: Dose-controlled supplementation of human cortical organoids with MGE-derived interneurons

Authors: *M. CASTELLANOS[1], L. VARGAS[1], E. NOEL[1], B. REES[1], J. KIM[1], D. JGAMADZE[2], S. ANDERSON[4], H. SONG[3], G.-L. MING[3], H.-C. I. CHEN[2]; [2]Neurosurg., [3]Neurosci., [1]Univ. of Pennsylvania, Philadelphia, PA; [4]Children's Hosp. of Philadelphia/UPenn, Philadelphia, PA

Abstract: Human cortical organoids are powerful stem cell-derived models of cortical development and hold promise as platforms for neural repair. However, current cortical organoids lack medial ganglionic eminence (MGE)-derived interneurons, which are essential for generating oscillations that coordinate network activity. Although assembloid-based approaches have been used to introduce these interneurons into cortical organoids, this strategy offers limited control over interneuron quantity and overall inhibitory tone. To address this limitation, we developed a centrifugation-based technique that enables dose-controlled interneuron supplementation. Human cortical organoids were generated from induced pluripotent stem cells and supplemented with dissociated MGE spheroid cells at graded doses (50,000, 100,000,

250,000, and 500,000 cells), alongside unmodified controls. Post-supplementation analyses were performed using immunohistochemistry and extracellular electrophysiology. Interneuron supplementation was well tolerated, with MGE cells maintaining healthy morphology across all organoids. Incorporation was dose-dependent, comprising 1.3% to 17.2% of total organoid cells across four escalating doses (n = 4-5 per dose), and was more consistent when a standardized suspension volume was delivered to each organoid rather than a standardized cellular concentration. Incorporated cells expressed GABA, Nkx2.1, and Lhx6, confirming MGE-derived interneuron identity. Additionally, preliminary analyses suggest a trend toward greater incorporation in organoids with lower rosette density, warranting further investigation into the role of host cytoarchitecture. Functionally, supplemented organoids exhibited spontaneous electrophysiologic activity at multiple timepoints between days 90 and 180 post-differentiation, with preliminary recordings suggesting more complex population burst activity compared to unsupplemented controls. Our findings establish a scalable platform for incorporating MGE-derived interneurons into human cortical organoids in a dose-controlled manner. Ongoing studies are examining the long-term maturation of supplemented interneurons and the temporal evolution of neural activity across doses.

Disclosures: M. Castellanos: None. **L. Vargas:** None. **E. Noel:** None. **B. Rees:** None. **J. Kim:** None. **D. Jgamadze:** None. **S. Anderson:** None. **H. Song:** None. **G. Ming:** None. **H.I. Chen:** None.

Nanosymposium

NANO06: Emerging Approaches to Study Human Development and Disease *In Vitro*

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO06.10

Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant R01 NS123849
NIH R21 CA279773
Alex's Lemonade Stand Foundation Innovation Grant

Title: ORION An open-source AI-assisted pipeline for reproducible brain organoid generation and multimodal electrophysiological characterization

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Abstract: Human brain organoids provide unique opportunities for studying early aspects of human neurodevelopment and disease mechanisms, but high inter-organoid variability and

fragmented analytical practices limit their translational use and cross-study validation. We developed Organoid Integrated Open Network (ORION), an open-source computational framework that captures and organizes all data and metadata for brain organoid generation and characterization from multi-electrode array (MEA) and patch-clamp recordings. We used ORION to characterize neuronal activity in telencephalic brain organoids with and without glioblastoma (GBM) across continuous 3-week recordings using an incubator-integrated MEA platform. We recorded from 16 control organoids and 8 GBM-organoid co-cultures across multiple stem cell and GBM lines. ORION integrates community tools to process electrical recordings and extract functional measurements for single-unit activity, functional connectivity, spectral decomposition, and phase-amplitude coupling (Fig. 1a).

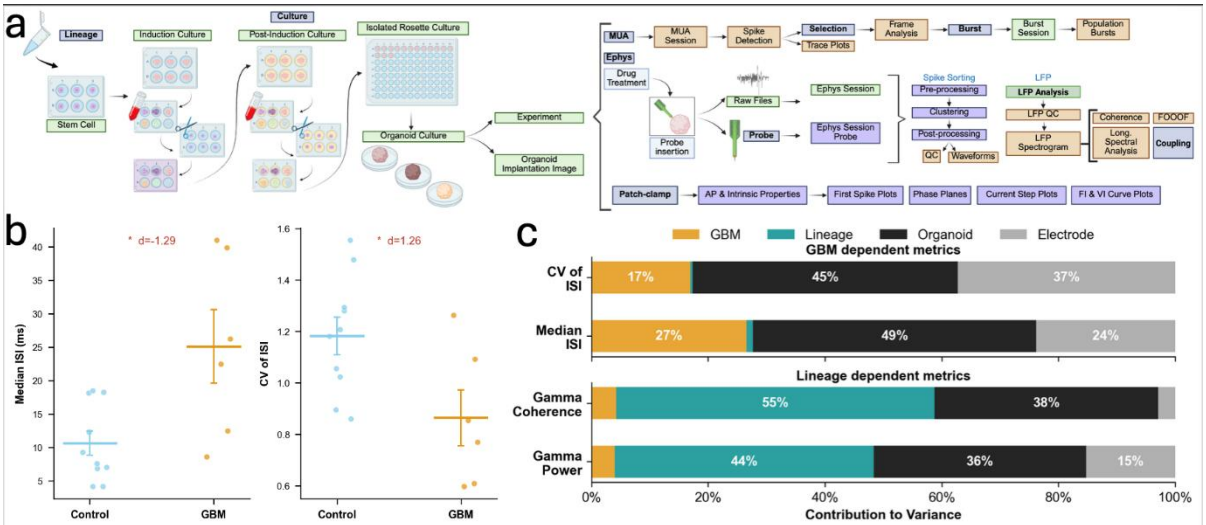


Figure 1: ORION computational framework for generating and characterizing brain organoids.

ORION-extracted measurements were analyzed using an AI-assisted framework that prioritizes and interprets MEA metrics based on prior electrophysiology literature. From this analysis, we observed reduced tonic spiking in the presence of GBM, evident from prolonged inter-spike intervals (ISIs), consistent with “tumor-core activity” described in non-proliferating tumor regions in patients and mice (Fig. 1b). To validate the chosen metrics, we used a linear mixed effects model that quantifies contributions of GBM status, stem cell lineage, and inter-organoid and inter-electrode variability to the observed variance (Fig. 1c). ORION provides a scalable, fully documented ecosystem that links organoid generation metadata with automated AI-assisted electrophysiology analysis and robust metric validation, accelerating the use of brain organoids as models for studying neural development and disease.

Disclosures: J. Werth: None. **M. Marín Alejo:** A. Employment/Salary (full or part-time):; DataJoint. **H. Ullah:** None. **M. Cuevas:** None. **T.T. Nguyen:** A. Employment/Salary (full or part-time):; DataJoint. **M. Godoy:** None. **J. Kubanek:** None. **D. Yatsenko:** A. Employment/Salary (full or part-time):; DataJoint. **A. Shcheglovitov:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.01

Topic: B.09. Glial Mechanisms

Title: Extracellular S100B secreted by astrocytes inhibits A-type potassium currents in dopaminergic neurons: Implications for Parkinson's Disease pathogenesis

Authors: *R. SRINIVASAN[1], S. RUFFINO[1], C. RODRIGUEZ[3], D. DAS[4], E. BANCROFT[2]; [1]Texas A&M Univ., College Station, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Univ., Houston, TX; [3]Texas A&M Univ. Syst. Hlth. Sci. Ctr., Bryan, TX; [4]Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: Among the many substances expressed and secreted by astrocytes, S100B is particularly relevant to neurodegeneration during Parkinson's Disease (PD). In this context, studies have shown that: (**i**) S100B is increased in the serum and CSF of PD patients, and S100B expression in the substantia nigra pars compacta (SNc) of PD patients is significantly higher than in healthy controls. (**ii**) A single nucleotide S100B gene polymorphism (SNP), rs9722 is associated with PD. (**iii**) Compared to healthy controls, PD patients show a 4-fold increase in autoantibodies against S100B five years after diagnosis. (**iv**) Overnight S100B elevation correlates with increased severity of PD symptoms. In addition, preclinical studies show that S100B ablation in mice protects against the mitochondrial neurotoxin, MPTP-induced dopaminergic (DA) neuron loss, while S100B overexpressing transgenic mice develop features of PD. These multiple clinical and preclinical studies provide compelling evidence that the secretion of S100B by astrocytes directly contributes to loss of SNc DA neurons, which is the proximate cause of PD. Based on these studies, we asked if acute extracellular application of S100B can cause abnormal alterations in the activity of DA neurons. We discovered that: (**i**) application of 50 pM S100B peptide to primary mouse midbrain cultures acutely inhibited A-type potassium currents only in DA neurons with no effect in non-DA neurons, and (**ii**) acute S100B-mediated inhibition of A-type potassium currents abnormally increased calcium influx via L-type voltage-gated calcium channels (VGCCs) only in DA neurons and not in non-DA neurons. Based on these findings, we created a novel AAV expressing a non-secreted version of S100B (non-sec-S100B) driven by the astrocyte-specific GfaABC1D promoter and examined the specific role of S100B secreted by SNc astrocytes in vivo on 6-hydroxydopamine-induced parkinsonism in mice. When compared to AAVs expressing full length secreted S100B (sec-S100B) in SNc astrocytes, mice with expression of non-sec-S100B in SNc astrocytes showed significantly decreased contralateral rotations with apomorphine. In addition, when compared to non-sec-S100B, sec-S100B expression in SNc astrocytes significantly reduced dopamine content, and also altered expression of A-type Kv4.3 channels in SNc DA neurons. Taken together, these data suggest that the secretion of S100B by astrocytes in the SNc during early PD directly contributes to pathologically altered SNc DA neuron activity.

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

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Presentation Number: NANO07.02

Topic: B.09. Glial Mechanisms

Support: NIH-NIMH (R01MH119355)
NIH-NIDA (R01DA048822)
Department of Defense (W911NF2110328)

Title: Dopaminergic Signaling Enhances Hippocampal Synaptic Plasticity Through Activation of Astrocytes

Authors: *A. ARAQUE, R. FALCON MOYA, J. NOEKER, C. BARBATO, C. BRUCH, D. GAO, P. KALAVA, D. KUMAR, I. SAMUEL, S. WINDRAM, P. KOFUJI;
Univ. of Minnesota, Minneapolis, MN

Abstract: Long-term synaptic changes are considered the major synaptic mechanisms underlying learning and memory. In the hippocampus, the coincidence of pre and postsynaptic activity in CA3-CA1 synapses triggers the long-term potentiation (LTP) of synaptic transmission. Dopamine (DA) is a key neurotransmitter involved in multiple physiological processes, including learning and memory. In the hippocampus, DA regulates LTP, but the exact mechanisms of this regulation are not fully elucidated. Astrocytes are currently considered important cells in brain function through the bidirectional signaling with neurons at tripartite synapses. Astrocytes respond with Ca^{2+} elevations to neurotransmitters and neuromodulators and release gliotransmitters that regulate synaptic function, network activity and animal behavior. Astrocytes responsiveness to DA has been reported in different brain areas. However, the responsiveness of hippocampal astrocytes to DA and their contribution to hippocampal synaptic plasticity remain largely unknown. We have investigated the DA-induced regulation of hippocampal LTP and the contribution of astrocytes to this phenomenon. We have used hippocampal slices, electrophysiological tools to record field synaptic potentials in CA1 evoked by stimulation of Schaffer collaterals (SC), chemogenetic activation of astrocytes and optogenetic stimulation of dopaminergic axons projecting from the ventral tegmental area (VTA) to the hippocampus. We have found: 1) Hippocampal astrocytes responded with calcium elevations to exogenously applied DA or optostimulation of DA axons. 2) Astrocyte responsiveness to DA was prevented by D1 receptor antagonists and was absent in transgenic mice lacking D1 receptors selectively in astrocytes ($aD1R^{-/-}$ mice), suggesting that the DA-evoked astrocyte calcium signal was mediated by activation of D1 receptors. 3) Pairing theta burst stimulation (TBS) of SC with DA application enhanced the LTP amplitude evoked by the TBS. 4) DA application in the absence of TBS did not induce long-term changes in synaptic transmission. 5) The DA-evoked LTP enhancement induced by paring TBS and DA was absent in $aD1R^{-/-}$ mice. 6) The DA-evoked LTP enhancement was absent in $IP3R2^{-/-}$ mice, in which astrocyte calcium signal is largely impaired. 7) Pairing TBS with chemogenetic stimulation of astrocytes selectively expressing GqDREADDs elicited LTP enhancement. We conclude that

dopaminergic signaling enhances hippocampal LTP through activation of D1 receptors in astrocytes.

Disclosures: A. Araque: None. **R. Falcon Moya:** None. **J. Noeker:** None. **C. Barbato:** None. **C. Bruch:** None. **D. Gao:** None. **P. Kalava:** None. **D. Kumar:** None. **I. Samuel:** None. **S. windram:** None. **P. Kofuji:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.03

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5F32NS119352
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NIH Grant 5R01NS124146
Helen Hay Whitney Postdoctoral Fellowship

Title: GPCR-dependent receptor trafficking gates astrocyte neurotransmitter responsiveness and dopamine circuit output

Authors: *K. GUTTENPLAN;
Vollum Inst., OHSU, Portland, OR

Abstract: Astrocytes powerfully regulate neuronal circuits, but which signals an astrocyte responds to and how those signals are converted into circuit modulation remains poorly defined. To address these questions, we imaged GCaMP6s in astrocytes (alrm-Gal4) of intact third-instar, mixed-sex larval ventral nerve cords ex vivo with tetrodotoxin. Astrocytes responded to tyramine and octopamine but not to dopamine, glutamate, acetylcholine, or GABA (n=6/condition). Within ~3 min of tyramine exposure, astrocytes acquired robust responses to all four neurotransmitters, an effect we term gating; vehicle and reverse-order (dopamine-first) controls showed no gating.
We next sought to determine the mechanism by which gating occurs in astrocytes. Astrocytic knockdown of the tyramine receptor Oct-TyrR abolished gating of every transmitter tested. Oct-TyrR stimulation induces calcium influx and reduces cAMP levels via Gαi. Comprable calcium influx via the TrpA1 did not induce gating, but blocking Gαi-mediated cAMP reduction (PTXa, Gαi RNAi) prevented gating. Further, the adenylyl cyclase inhibitor SQ22536, but not forskolin, was sufficient to gate dopamine. To determine how cAMP reduction induced dopamine responsiveness, we knocked down each of the four fly metabotropic dopamine receptors. Only Dop2R knockdown blocked dopamine gating, and inhibiting receptor internalization (a known target of cAMP regulation) with CMPD101 gated dopamine without affecting glutamate or acetylcholine.

What effect does gated dopamine responsiveness have on circuit activity? While dopamine reduced Ddc+ dopaminergic neuron activity, CMPD101 pretreatment inverted this into a ~2-fold increase, a reversal abolished by astrocyte-specific Dop2R knockdown. This suggests that astrocyte dopamine responses can reverse the effect of dopamine on downstream neuronal circuits. Astrocytic Dop2R knockdown (two RNAi lines, with elav-Gal80) also delayed larval righting without altering crawling speed, showing that this circuit effect manifested as a disruption in whole animal behavior. Finally, we demonstrated in primary rat cortical astrocytes (p7, mixed sex) loaded with Fluo-4 that NE exposure, α2 agonist UK14304 exposure, SQ22536-mediated cAMP reduction, and CMPD101-mediated internalization inhibition each gated subthreshold dopamine responses in mammalian astrocytes. Thus, astrocytes can regulate their neurotransmitter sensitivity through Gαi-dependent receptor surface retention, a conserved mechanism that redirects circuit output and behavior.

Disclosures: K. Guttenplan: None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.04

Topic: B.09. Glial Mechanisms

Support: NIH Grant R35NS132326

Title: Satellite microglia gate neuronal excitability by displacing inhibitory synapses in adult brain

Authors: *S. ZHAO[1], M. FEI[2], J. ZHENG[2], C. MAI[2], T. CHRISTENSEN[1], D. KLEIDONAS[2], Y. LIANG[2], F. QI[1], K. HARUWAKA[2], L. WANG[1], G. A. WORRELL[1], A. NGUYEN[1], L.-J. WU[2];
[1]Mayo Clin., Rochester, MN; [2]Ctr. for Neuroimmunology and Glial Biology, Inst. of Mol. Medicine, Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Microglia, the primary immune cells of the central nervous system, are known for sculpting excitatory neural circuits via dynamic processes. However, their role in modulating inhibitory synaptic connections in adulthood remains largely unexplored. In this study, we identified an underappreciated microglia subpopulation, satellite microglia with physical soma-soma contact with neurons, that reshape inhibitory circuit connectivity and gate neuronal activity by displacing inhibitory synapses in the adult mouse brain. Using chronic in vivo two-photon imaging in adult mice, we observed in real time that satellite microglia associations displaced perisomatic inhibitory synapses whereas their dissociation permitted inhibitory synaptogenesis. Redistribution of satellite microglia reorganized inhibitory connectivity, altered local neural networks and changed behaviors. These findings establish satellite microglia as key architects of inhibitory circuitry and suggest their broader role in neural plasticity in health and disease.

Disclosures: S. Zhao: None. **M. Fei:** None. **J. Zheng:** None. **C. Mai:** None. **T. Christensen:** None. **D. Kleidonas:** None. **Y. Liang:** None. **F. Qi:** None. **K. Haruwaka:** None. **L. Wang:** None. **G.A. Worrell:** None. **A. Nguyen:** None. **L. Wu:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Presentation Number: NANO07.05

Topic: B.09. Glial Mechanisms

Title: Sex-specific diurnal changes in astrocytes within the mouse substantia nigra pars compacta and its implications for Parkinson's disease

Authors: *D. DAS[1], C. RODRIGUEZ[2], K. G. LINARES[3], E. BANCROFT[4], R. SRINIVASAN[5];
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Abstract: Astrocytes are key regulators of neuronal function, influencing neurotransmitter reuptake, calcium signaling, and the release of ATP and cytokines. These processes depend on brain region-specific astrocyte-neuron interactions. We previously showed that in the mouse substantia nigra pars compacta (SNc), S100B labeled astrocytic processes completely envelope the somata of tyrosine hydroxylase (TH) expressing dopaminergic (DA) neurons. In this study, we assessed if this unique morphological relationship between astrocytic processes and DA somata in the SNc changes in a diurnal and sex-dependent fashion. 3-4-month-old male and female C57BL/6 mice, exposed to a 12:12 h light-dark cycle, were transcardially perfused at Zeitgeber Time (ZT) 3 and ZT 15. At ZT 15 compared to ZT 3, wrapping of S100B-containing astrocytic processes around SNc DA somata was significantly decreased by ~50% only in male mice, corresponding with time-dependent changes in S100B astrocytic process density only in males. This diurnal structural plasticity correlated with diurnal changes in SNc dopamine content in both astrocytic and extra-astrocytic compartments. In male mice, diurnal morphological changes in SNc astrocyte processes also correlated with alterations in acetylcholine-evoked dopamine release at axonal terminals within the dorsolateral striatum (DLS). Diurnal changes in SNc serotonin (5-HT) levels led us to investigate 5-HT6 receptors (5-HT6Rs) as potential mediators. We found ~50% more 5-HT6R punctae in SNc astrocytes in male mice at ZT 15 than ZT 3. In mouse primary midbrain neuron-astrocyte co-cultures expressing 5-HT6Rs, 5-HT administration changed actin dynamics *in vitro*, which could be inhibited by pre-treatment with the selective 5-HT6R antagonist SB 399885. Intraperitoneal injection of SB 399885 12 hours prior to perfusion significantly decreased astrocytic wrapping and process density at ZT 3, altered TH mean intensity patterns between timepoints, and disrupted dopamine release at DA axonal terminals in the DLS. Knockdown of astrocyte-specific 5-HT6Rs in the SNc resulted in

~45% fewer 5-HT6R puncta in the injected SNc at ZT3 and ~50% decreased wrapping of S100B-expressing astrocyte processes around SNc DA neurons at ZT3 compared to the uninjected side. Together, these data suggest that diurnal changes in astrocyte process density proceed via 5-HT6Rs expressed in SNc astrocytes and may affect dopamine release in the DLS in male mice, with important implications for understanding diurnal and sex-specific differences in Parkinson's disease pathogenesis.

Disclosures: D. Das: None. **C. Rodriguez:** None. **K.G. Linares:** None. **E. Bancroft:** None. **R. Srinivasan:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.06

Topic: B.09. Glial Mechanisms

Support: Weill Neurohub Fellowship
NIH R01MH135137

Title: When too much is not enough: an unexpected role for interferon signaling in a mouse model of Down syndrome

Authors: *S. R. ANDERSON[1,2], P. CHIARANUNT[3], A. V. MOLOFSKY[4];
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Abstract: Interferons (IFNs) are classic antiviral cytokines with emerging roles in neurodevelopment, and their dysregulation is linked to several neurodevelopmental disorders. Down syndrome (DS), the leading genetic cause of intellectual disability, involves triplication of both type I IFN receptor subunits, leading to hyperactive IFN signaling and peripheral immune dysfunction. DS thus provides a genetically defined model to mechanistically interrogate how IFN-I signaling impacts brain development. Using the Dp(16)1Yey/+ (Dp16) mouse model, we identified microglia, endothelial cells, and border-associated macrophages as the predominant IFN-I responders in the developing forebrain by single-cell RNA sequencing. Using our novel IFN-I reporter (IFN-brite), we found increased IFN-responsive microglia and neurons in the developing Dp16 brain. Behaviorally, we observed Dp16 animals exhibit increased ultrasonic vocalizations in response to maternal separation, reduced locomotion and rearing, and more restricted behavioral patterns measured by motion sequencing (MoSeq). JAK-STAT inhibition (baricitinib) and genetic copy number rescue of IFN-I receptor dosage (Dp162xIFNAR1) failed to improve, and in some cases exacerbated, these behavioral phenotypes. Unexpectedly, AAV-mediated enhancement of CNS IFN-I signaling was beneficial, partially rescuing vocalization phenotypes. However, this effect was dose-dependent, as hyper-physiological IFN-I levels

caused cortical thinning, apoptosis, and gliosis reminiscent of classic type I interferonopathies. To test the role of IFN-I in circuit remodeling in the Dp16, we performed whisker deprivation, which induces expansion of IFN-responsive microglia in the somatosensory cortex. Dp16 cortical microglia, despite mildly elevated baseline IFN-I signaling, failed to mount appropriate IFN-I responses during experience-dependent circuit remodeling. Together, our data reveal a physiologic "goldilocks zone" of IFN-I signaling that promotes healthy brain development in this DS mouse model. This raises the question of whether enhancement, rather than inhibition of IFN-I signaling, may be therapeutically beneficial for some neurodevelopmental disorders.

Disclosures: S.R. Anderson: None. **P. Chiaranunt:** None. **A.V. Molofsky:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.07

Topic: B.09. Glial Mechanisms

Support: NIH Grant NS119243
NIH Grant 5T32HL007284-49
Owens Family Foundation

Title: Sex Differences in Somatosensory Circuitry are Programmed by Developmental Microglia-Astrocyte Interactions

Authors: *A. HUGHES, U. B. EYO;
Univ. of Virginia, Charlottesville, VA

Abstract: Men possess a greater density of cortical synapses in the adult brain relative to women, but the underlying mechanism and functional significance of this sex difference is unclear. While microglia and astrocytes have been identified as key regulators of synapse production and elimination in the developing brain, it remains unknown whether sex differences in the activity of these glial cells may contribute to sex-specific synaptic phenotypes and, as such, contribute to male- and female-specific neural circuit activity in development and adulthood. Here, we identify a greater density of excitatory synapses in the male mouse somatosensory cortex (S1) which emerges between P10 and P15 and persists into the adult brain. We show that increased phagocytic activity in microglia of female mice causes a greater engulfment of astrocytes in the female S1 in a MERTK-dependent manner during a discrete developmental window from P12 to P17. Additionally, we demonstrate that these sex differences are regulated at least in part by estrogen signaling. The resulting greater astrocyte density in males corresponds with an increase in astrocyte-derived synaptogenic factors including hevin and thrombospondin-2 in the developing male S1, which we propose leads to the observed sex difference in S1 synapse density during this time window. Moreover, we demonstrate that this sex difference in synapse density correlates with an increase in neuronal activity in the male S1

both in development and adulthood. These results demonstrate an indirect mechanism whereby sex differences in microglial activity regulate astrocyte density and activity, which in turn regulate S1 synapse density and neuronal activity. These findings could be relevant for neurodevelopmental and neuropsychiatric disorders such as autism spectrum disorders (ASD), characterized by sex biases in diagnosis, synaptic abnormalities, and glial-immune dysfunction during development.

Disclosures: A. Hughes: None. **U.B. Eyo:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.08

Topic: B.09. Glial Mechanisms

Support: R35NS132326
R01AG041274

Title: Astrocyte-to-microglia purinergic signaling mediates synaptic shielding and promotes neuronal activity

Authors: *K. HARUWAKA[1], J. LIU[2], Y. LIANG[1], S. MATSUMOTO[1], D. KLEIDONAS[1], W. SHI[1], S. ZHAO[1], Z. XIE[3], M. JING[2], L.-J. WU[1];
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Abstract: Microglia regulate neuronal circuits across diverse activity states. In neuronal hyperactivity, extracellular adenosine triphosphate (ATP) and related purinergic signals recruit microglial processes to overactive or injured neural elements, where microglia can limit excessive activity. By contrast, how microglia respond to neuronal hypoactivity and whether purinergic signaling contributes to circuit regulation in this opposite state remains poorly understood. We previously showed that, during isoflurane anesthesia, microglial processes shield perisomatic inhibitory inputs onto excitatory neurons and promote rebound neuronal activity during emergence. However, the local signal that directs microglia to selected inhibitory synaptic sites remained unknown. Here, we investigated how cortical hypoactivity induces synaptic shielding by microglia in the mouse cortex. Using in vivo two-photon imaging with genetically encoded extracellular ATP and calcium sensors, surprisingly we found that isoflurane anesthesia induced spatially confined ATP release during neuronal suppression and early emergence. These ATP events occurred near neuronal somata and parvalbumin-positive boutons, and were followed by long-lasting bulbous endings (BEs). Pharmacological inhibition of pannexin 1 (PANX1) and astrocyte-specific Panx1 deletion reduced anesthesia-induced ATP release,

indicating that astrocytic PANX1 is required for this ATP signal. PANX1 signals and localized astrocytic Ca^{2+} events were positioned near inhibitory synaptic markers, suggesting a peri-inhibitory astrocytic ATP source. We further found that microglial P2Y12 signaling converted local ATP events into persistent BEs with compartmentalized microglial Ca^{2+} activity. P2Y12-deficient microglia formed transient BE-like swellings but failed to stabilize ATP-associated BEs, and microglia-specific P2Y12 deletion abolished the rebound increase in neuronal Ca^{2+} activity during emergence. Finally, chemogenetic suppression of excitatory neurons and natural sleep also increased local ATP events and microglial BE formation. These findings reveal that ATP-P2Y12 signaling is not limited to microglial responses to neuronal hyperactivity, but also operates during neuronal hypoactivity through an astrocyte-to-microglia pathway. We propose that astrocytic ATP provides a local positional cue that converts hypoactivity into microglial P2Y12-dependent synaptic shielding, thereby enabling synapse-selective regulation of circuit output.

Disclosures: K. Haruwaka: None. **J. Liu:** None. **Y. Liang:** None. **S. Matsumoto:** None. **D. Kleidonas:** None. **W. Shi:** None. **S. Zhao:** None. **Z. Xie:** None. **M. Jing:** None. **L. Wu:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.09

Topic: B.09. Glial Mechanisms

Support: NIH Grant R01NS133047
3R01NS133047-01S1

Title: The role of astrocytes and microglia during development of visually triggered defensive behaviors

Authors: G. ALBRECHT[1], R. RAMIREZ[1], D. MORADPOUR[1], J. MAR[2], ***I. FARHY-TSELNICKER**[1];
[2]TAMIN, [1]Texas A&M Univ. - Site 2, College Station, TX

Abstract: Visually evoked defensive behaviors such as freezing or escaping are reactions exhibited by animals in response to a threatening stimulus, such as a looming predator. These behaviors are conserved across numerous species including rodents and humans and involve complex coordination between circuits spanning multiple brain regions to initiate and maintain the diverse responses. Though escape from danger is an innate behavior, discerning between threatening and harmless stimuli must be acquired through life experience and responses adapted accordingly. Conditions such as chronic or early life stress, or anxiety can induce disproportionate responses, perturbing normal development of defensive behaviors with long lasting repercussions. Yet how defensive responses are established in developing animals, and the role of astrocytes and microglia in regulating this process, is largely unknown. We analyzed

defensive responses to a visual looming threat across development in both male and female mice and quantified changes of neuronal synapses, astrocytes, and microglia in relevant brain regions, sSC and dPAG. Our behavioral analysis showed that adolescent mice (4 weeks old) primarily escape from the visual threat, while adults (2-4 months old) exhibited mainly freezing. Further, we observed that animals rapidly adapt to the looming stimulus and that adult females are more responsive than males. These age-dependent behaviors correlated with dynamic changes in both glutamatergic and GABAergic synapse, astrocyte, and microglia numbers in the dPAG, suggesting its involvement in the developmental switch from escaping to freezing. Moreover, perturbing synapse formation or astrocyte function using genetic knockout mouse models resulted in disrupted defensive responses. Taken together, our findings reveal age- and sex-specific responses to visual threats and suggest a potential role for glia in the development of these behaviors. Current and future work is focused on region specific perturbations of synaptic and glial proteins in the sSC and dPAG, and analysis of additional threat response types and brain regions involved.

Disclosures: G. Albrecht: None. **R. Ramirez:** None. **D. moradpour:** None. **J. Mar:** None. **I. Farhy-Tselnicker:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.10

Topic: B.09. Glial Mechanisms

Support: R01HL104101

Title: Distinct RTN astrocyte subpopulations are differentially affected by MeCP2 deficiency

Authors: *S. JAHANBANI[1], D. K. MULKEY[2], M. L. OLSEN[3];
[1]Virginia Tech. Neurosci. PhD Program, Blacksburg, VA; [2]Dept. Physiol. and Neurobio., Univ. of Connecticut Physiol. & Neurobio., Storrs Manfld, CT; [3]Virginia Tech., Blacksburg, VA

Abstract: Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder caused by mutations in methyl-CpG-binding protein 2 (*MeCP2*). RTT is characterized by cognitive, motor, and respiratory dysfunction, and impaired respiratory chemoreception is thought to contribute to disordered breathing and cardiorespiratory arrest. Neurons and astrocytes within the retrotrapezoid nucleus (RTN), a key respiratory chemoreceptor region, contribute to the CO_2/H^+-dependent drive to breathe. To determine how *MeCP2* deficiency alters RTN astrocyte biology, we performed single-cell RNA sequencing of RTN tissue from wild-type and *MeCP2*-deficient rats. Analysis identified two transcriptionally distinct astrocyte populations in both genotypes. In WT animals, one astrocyte subcluster was enriched for metabolic support, ion homeostasis, and neurotransmission signaling, whereas the second astrocyte subcluster was enriched for extracellular matrix organization, adhesion, cytoskeletal remodeling, and pial surface-associated

functions. Immunohistochemistry, confocal imaging, and 3D reconstruction confirmed distinct localization and morphology, with surface astrocytes exhibiting elongated radial-like processes and parenchymal astrocytes displaying complex morphology. Both populations were preserved in *MeCP2*-deficient rats but exhibited differential vulnerability to *MeCP2* loss. Parenchymal astrocytes showed reduced expression of genes involved in metabolic support, ion homeostasis, and neurotransmission. In contrast, RTN surface astrocytes displayed substantially greater transcriptional disruption, with widespread alterations in extracellular matrix, adhesion, cytoskeletal, developmental, synaptic organization, and intercellular signaling pathways, together with increased enrichment of protein synthesis and ribosome biogenesis programs. These findings reveal astrocyte heterogeneity within the RTN and demonstrate that *MeCP2* deficiency disrupts specialized astrocyte programs in a subtype-specific manner that may impair astrocyte-mediated regulation of respiratory networks and contribute to breathing abnormalities in RTT.

Disclosures: S. Jahanbani: None. **D.K. Mulkey:** None. **M.L. Olsen:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Presentation Number: NANO07.11

Topic: B.09. Glial Mechanisms

Support: Whitehall Research Grant 2021-08-025
NIH Grant DP2NS136871

Title: Dynamic Changes of Cortical Astrocytes During Motor Skill Learning

Authors: E. KANG[1], T. MA[2], Z. KOU[3], ***X. YU**[1];
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Abstract: The ability to acquire new knowledge and skills and retrieve information is a fundamental feature of the brain that becomes deranged in numerous neurological and psychiatric disorders. Understanding the principles of learning and memory has thus been one of the critical questions in neuroscience. Compared with explicit (declarative) memory for facts and events, less is known about the mechanisms of implicit (procedural) memory for motor skills. Previous studies demonstrated that substantial remodeling of synaptic connections in the mouse primary motor cortex (M1) occurred during motor skill learning, providing a structural basis for enduring motor memory. However, the neurobiological substances modulating this process remain incompletely defined. As abundant non-neuronal cells, astrocytes tile the entire brain and form close contacts with neurons and other glial cells. Increasing evidence has supported the significance of astrocyte calcium signaling in regulating neural circuit function and various aspects of behaviors. In this study, we examined the temporal and spatial dynamics of astrocyte calcium signals in the M1 at different stages of motor skill learning with repetitive two-photon *in*

vivo imaging. Using machine learning-based analysis, we further found that astrocyte calcium signals encode information predictive of improved motor performance. These findings suggest that astrocytes play an active role in motor learning and may contribute to the information storage for long-lasting motor memories.

Disclosures: E. Kang: None. **T. Ma:** None. **Z. Kou:** None. **X. Yu:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Presentation Number: NANO07.12

Topic: B.09. Glial Mechanisms

Support: R21NS140788
R01NS116059

Title: Dependence of potassium and neurotransmitter uptake on astrocyte syncytial isopotentiality

Authors: *S. TIMSINA[1], M. ZHOU[2];
[1]The Ohio State Univ., Columbus, OH; [2]Dept. of Neurosci., Ohio State Univ., Columbus, OH

Abstract: Timely removal of K^+ and neurotransmitters following neuronal excitation and synaptic transmission is vital for continued CNS function. Astrocytes are uniquely equipped to perform these homeostatic tasks through abundantly expressed inwardly rectifying $K_{ir}4.1$ K^+ channels and Na^+-dependent glutamate and GABA transporters (GLT-1 and GAT-3, respectively). Efficient uptake, however, requires a sustained electrochemical driving force, and astrocytes achieve this through gap junctional coupling into an isopotential network, termed syncytial isopotentiality (SI). SI is a fundamental prerequisite for K^+ and neurotransmitter uptake by preventing membrane potential (V_M) depolarization, thereby sustaining the electrochemical driving force for uptake. However, direct experimental evidence to support this notion is still lacking. To address this question, local puffs (10 ms) of high K^+ (6 mM), glutamate (1 mM), and GABA (1 mM) were applied to hippocampal astrocytes in acute brain slices during whole-cell patch-clamp recordings. In voltage-clamp recordings, 66.6% of the high K^+-induced uptake current was eliminated by 100 μM Ba^{2+}, a selective blocker for $K_{ir}4.1$. Glutamate and GABA uptake currents were readily identified in the presence of antagonists for astrocytic ionotropic glutamate and $GABA_A$-R receptors. We next examined the role of SI in maintaining the driving force for K^+ and neurotransmitter uptake in current-clamp recordings. Application of high K^+, glutamate, or GABA produced only modest membrane depolarization when astrocyte syncytial coupling was intact, indicating that the electrochemical driving force for uptake was preserved. In contrast, disruption of SI by the gap junction blocker Meclofenamic acid (100 μM) resulted in a large depolarization of the astrocyte $V_{M,}$ indicating a rapid dissipation of the uptake driving

force. Thus, these findings are the first to experimentally demonstrate the dependency of K^+, glutamate, and GABA uptake on astrocyte syncytial coupling into an isopotential network.

Disclosures: S. Timsina: None. **M. Zhou:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO07.13

Topic: B.09. Glial Mechanisms

Support: Weill Cornell Medicine and generous support from the Swid Family

Title: Astrocytic mGluR3 induces sex-specific effects on hippocampal synaptic function and memory

Authors: *M. JANG, A. WHYE, A. L. ORR, A. G. ORR;
Weill Cornell Med., New York, NY

Abstract: The hippocampus is a key brain region underlying cognition and behavior. In addition to neurons, astrocytes play critical roles in synaptic and circuit mechanisms required for cognitive processes, including learning and memory. Although hippocampal function and behavior are known to have sex-specific features in health and disease, it is not clear if and how astrocyte signaling might contribute to sex differences in brain function. We previously reported that astrocytic metabotropic glutamate receptor 3 (mGluR3), a major $G_{i/o}$-coupled glutamate receptor enriched in astrocytes and a top reduced astrocytic transcript in aging and Alzheimer's disease-associated pathology, regulates memory in a sex-specific manner. In vivo gene editing revealed that reducing mGluR3 levels in hippocampal astrocytes is sufficient to impair memory in females but not males, and that enhancing astrocytic mGluR3 levels improves memory in females but not males. Further, acute chemogenetic stimulation of astrocytic $G_{i/o}$-coupled or G_s-coupled receptors induced divergent and sex-specific effects on memory. However, the mechanisms underlying the effects of mGluR3 reduction remain undefined. Thus, we generated conditional astrocyte-targeted mGluR3 knockout (cKO) mice and conducted behavioral and electrophysiological analyses and calcium imaging using a genetically encoded calcium sensor. We found that female cKO mice recapitulated the previously reported sex-specific effects by showing spatial and contextual memory loss, which was not detected in cKO males. Electrophysiological analyses revealed changes in hippocampal synaptic plasticity and presynaptic neurotransmitter release in female but not male cKO mice. These synaptic effects in females were accompanied by dysregulated astrocytic calcium signaling, implicating a novel female-specific intracellular signaling mechanism underlying the roles of mGluR3 in hippocampal astrocytes. Our findings suggest that astrocytic mGluR3 is a key regulator of hippocampal synaptic function in females and further highlight astrocytic G protein-coupled signaling as a sex-dependent therapeutic target for cognitive dysfunction.

Disclosures: M. Jang: None. **A. Whye:** None. **A.L. Orr:** None. **A.G. Orr:** None.

Nanosymposium

NANO07: Glial Mechanisms of Synaptic and Circuit Function

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Presentation Number: NANO07.14

Topic: B.09. Glial Mechanisms

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DoD Grant W911NF-21-1-0312
NARSAD Young Investigator Award 28616
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Title: Glial underpinnings of norepinephrine neuromodulation of synapses

Authors: *T. PAPOUIN;
Neurosci., Washington Univ. in St Louis, St. Louis, MO

Abstract: Locus ceruleus (LC)-derived norepinephrine (NE) drives network and behavioral adaptations to environmental saliencies by reconfiguring circuit functional connectivity, but the underlying synapse-level mechanisms are elusive. In this work, we showed that NE remodeling of synaptic function is completely independent from its binding on neuronal receptors. Instead, astrocytic α1a adrenergic receptors (α1a-AR) and astrocyte calcium dynamics fully gate the effect of NE on synapses. Additionally, we found that NE suppression of synaptic strength results from an adenosine 5′-triphosphate (ATP)-derived and A1 adenosine receptor-mediated control of presynaptic efficacy. These findings suggest that astrocytes are a core component of neuromodulatory systems and the circuit effector through which NE produces network and behavioral adaptations

Disclosures: T. Papouin: None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.01

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

Support: Alzheimer's Association Research Fellowship (AARF-23-1150672)
CureAlz Fund

Title: Immune Signatures of Vulnerability and Resilience in Alzheimer Disease

Authors: ***S. KUMAR**[1,2], C. Z. KLEIN[1], C. AGUERO MURILLO[1,2], P. AGUERO[1], P. LUENGO MARTIN[1], C. BIANCO[1], T. GOMEZ-ISLA[1,2];
[1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA

Abstract: Background: Neuroinflammatory processes mediated by microglia and peripheral immune cells are increasingly implicated in Alzheimer disease (AD), yet their relationship to neuropathological stage and clinical expression remains unclear. Disease-associated microglia (DAM) are linked to amyloid-β and tau pathology and may contribute to the recruitment of peripheral immune cells into the brain. However, immune activation profiles across defined stages of AD neuropathologic change (ADNC), particularly in individuals with substantial pathology in the absence of dementia (resilient), remain poorly defined. **Methods:** Fifty-one postmortem human brains were categorized into four groups: demented Braak V-VI, demented Braak III-IV, non-demented Braak III-IV (resilient), and cognitively normal controls with absent or minimal ADNC. Cases with coexisting synucleinopathy, TDP-43 pathology, or significant cerebrovascular disease were excluded. Quantitative immunohistochemistry was performed in entorhinal cortex sections to assess amyloid plaque burden, phosphorylated tau (p-Tau), CD11c-positive DAM, and CD8-positive T-cell infiltration. **Results:** Amyloid and p-Tau burdens were significantly elevated in both demented groups compared with controls and were similar between demented and resilient Braak III-IV cases. In contrast, demented individuals showed marked increases in CD11c-positive DAM burden in gray and white matter and elevated parenchymal CD8-positive T-cell infiltration relative to controls. Resilient Braak III-IV cases exhibited significantly reduced DAM accumulation and T-cell infiltration compared with demented individuals at the same pathological stage. **Conclusions:** Dementia in AD is associated with robust microglial activation and peripheral immune infiltration across neuropathological stages, whereas resilient individuals with equivalent amyloid and tau burden exhibit an attenuated neuroimmune response. These findings suggest that neuroimmune activation, rather than neuropathological load alone, may contribute to the clinical expression of dementia in AD. Ongoing work aims to define how central and peripheral immune responses modulate synaptic and neuronal vulnerability across disease progression.

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Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.02

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

Title: Understand and Target the Brain-Peripheral Immune Loop to Stop Alzheimer's Disease

Authors: *L. CALVIER, J. HERZ;
UT Southwestern Med. Ctr., Dallas, TX

Abstract: Alzheimer's disease (AD) is associated with blood-brain barrier (BBB) dysfunction, neuroinflammation, and cognitive decline, but the signals linking amyloid pathology to sustained peripheral immune activation remain poorly understood. Reelin is a large extracellular glycoprotein best known for its roles in neuronal development and synaptic plasticity. Here, we identify circulating Reelin as a pathogenic mediator of neurovascular dysfunction in AD. Plasma Reelin levels were elevated in AD patients and multiple amyloid mouse models, including 5xFAD and APP^NL-F mice. Increased Reln expression was observed in skull bone marrow and was associated with local immune activation. Intracerebral Aβ42 administration increased skull marrow Reln expression and circulating Reelin, while reduction of Aβ42 through γ-secretase modulation lowered plasma Reelin levels. Reelin was detected in skull but not femoral bone marrow, supporting a localized brain-to-skull communication pathway. Mechanistically, recombinant Reelin activated endothelial cells through ApoER2-dependent signaling, increased expression of E-selectin, ICAM-1, and VCAM-1, promoted leukocyte adhesion and transmigration, and disrupted endothelial barrier integrity through LIMK-Cofilin-mediated cytoskeletal remodeling. In vivo, elevated circulating Reelin was associated with increased leukocyte rolling, BBB leakage, neuroinflammation, and cognitive impairment. Therapeutically, peripheral neutralization of circulating Reelin using the function-blocking antibody CR-50 restored BBB integrity, reduced leukocyte-endothelial interactions, attenuated neuroinflammation, improved cognitive performance, and lowered plasma neurofilament light levels in amyloid mouse models. Unexpectedly, anti-Reelin treatment also reduced established amyloid plaque burden in advanced disease. Together, these findings identify circulating Reelin as a mechanistically defined regulator of BBB dysfunction and neuroinflammation in AD and suggest that targeting peripheral Reelin may represent a novel therapeutic strategy to restore neurovascular homeostasis and modify disease progression.

Disclosures: L. Calvier: None. **J. Herz:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.03

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

Support: the National Natural Science Foundation of China (82220108009, 82201568, 82401407)
STI2030-Major Projects (2021ZD0201801)
the National Key R and D Program of China (2022YFC3602600, 2021YFA1101402)

Title: A novel TREM2 mutation reveals peripheral-to-central pathological protein infiltration in Alzheimer's disease

Authors: *H. YANG;
Dept. of Neurol. & Innovation Ctr. for Neurolog. Disorders, Xuanwu Hospital, Capital Med., Beijing, China

Abstract: We identify a novel start codon missense mutation in *TREM2* (*TREM2*$^{c.3G>A}$, M1I) that causes complete loss of TREM2 expression and is associated with early-onset dementia in humans. *Trem2*$^{c.3G>A}$ mice exhibited aberrant cerebral accumulation of peripherally derived proteins, including β2-microglobulin, alongside exacerbated amyloid burden, premature hyperphosphorylated tau, and cognitive deficits, positioning peripheral protein infiltration as an early contributor to central pathology. Mechanistically, TREM2 loss activates NF-κB signaling in microglia, driving sustained CCL2 upregulation that activates endothelial cell CCR2, thereby compromising the structural integrity of the cerebrovasculature and facilitating the cerebral accumulation of peripherally derived proteins. Pharmacological CCR2 inhibition and endothelial cell-specific *Ccr2* deletion restored cerebrovascular integrity, attenuated amyloid burden, and ameliorated cognitive deficits. Our findings establish a novel mechanistic link between microglial dysfunction, cerebrovascular compromise, and peripheral pathological protein infiltration, identifying the CCL2-CCR2 axis as a candidate therapeutic target in TREM2-associated neurodegeneration.

Disclosures: H. Yang: None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

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Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.04

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

Support: Swiss National Science Foundation (grant 310030_212322)

Title: Targeting and inhibiting TSPO improves Alzheimer's disease pathology.

Authors: A. BADINA[1], E. RAVELOSON[1], K. CEYZÉRIAT[2], L. ABJEAN[1], S. TSARTSALIS[1], P. MILLET[3], ***B. B. TOURNIER**[3];
[1]Univ. of Geneva, Geneva, Switzerland; [2]CIBM Ctr. for Biomed. Imaging, Univ. of Geneva, Etrembières, France; [3]Univ. of Geneva / Univ. Hosp. of Geneva, Geneva, Switzerland

Abstract: Alzheimer’s disease (AD) is a chronic neurodegenerative disorder accounting for over 70% of dementia cases. As dementia currently affects around 45 million people worldwide, with cases expected to triple by 2050, AD represents a major challenge. AD is characterized by cognitive decline associated with impaired cerebral metabolism, neuroinflammation, and the accumulation of β-amyloid (Aβ) and hyperphosphorylated Tau. Increased glial reactivity,

reflected by overexpression of the 18 kDa translocator protein (TSPO), is also widely reported.We investigated the effects of both genetic (KO) and pharmacological TSPO inhibition. Chronic pharmacological treatment was performed in 15-month-old WT, 3xTg-AD (Tg) and Tg.TSPO-KO mice through the administration of a TSPO ligand in drinking water for 4 months. A multi-scale approach was used to assess impact through cognition (Y-maze test), cellular activity (in vivo glucose uptake by PET with FDG and cell density surrounding Aβ plaques), and molecular alterations (bulk proteomic and transcriptomic analysis of FACS-sorted astrocyte and microglial populations) in 19-month-old mice.Genetic TSPO inhibition improved cognitive performance in Tg mice, demonstrating its therapeutic potential. This effect was associated with a restoration to normal of glucose uptake. At the molecular level, transcriptomic rescue analysis revealed that TSPO KO normalized the expression of 75% and 49% of dysregulated genes in astrocyte and microglial populations, respectively, and involved neuroinflammatory and oxidative stress-related pathways. In contrast, Aβ and Tau levels were not altered by genetic TSPO inhibition.Pharmacological inhibition also improved the pathological phenotype of Tg mice, which do not develop cognitive decline. The treatment restores normal glucose uptake, further supporting optimized astrocyte-neuron communication. Around Aβ plaques, the density of reactive astrocytes is increased in Tg versus WT mice but is reduced by the treatment. Microglial activation remains elevated in the vicinity of plaques and is not affected by the treatment. The protein CRYAB, which inhibits protein aggregation, appears to be a relevant functional target, as its reduced expression in Tg mice is normalized by treatment, and, with the observation of a reduction in Aβ density.The integrated analysis of both approaches suggests that TSPO inhibition primarily exerts its beneficial effects through glial modulation, leading to reduced neuroinflammation and oxidative stress, improved metabolic function, and enhanced astrocyte-neuron communication, rather than through direct effects on amyloid or tau pathology.

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Nanosymposium

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Presentation Number: NANO08.05

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

Support: AG065992
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P30 AG050886
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UAB startup funds 3123226

Title: Microbiome Integrity Protects Against Glial-Mediated Tau and Amyloid Pathology Through Circadian and Autophagy Homeostasis

Authors: *K. MADAMANCHI[1], S. REDDY[1], J. WATSON[1], G. MELKANI[2,1];
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Abstract: Alzheimer's disease (AD) is characterized not only by tau and amyloid-*β* (a*β*) aggregation but also by systemic disruptions in circadian rhythms, metabolism, and gut-brain communication that exacerbate neuroinflammation and neurodegeneration. While glial cells play central roles in inflammatory signaling and proteostasis, the contribution of the gut microbiome to glia-driven AD pathology remains poorly understood. Here, we used *Drosophila* models with glial-specific expressions of human tau and amyloid-associated transgenes to investigate how microbiome integrity influences disease progression. AD models exhibited significant shifts in brain and gut microbial composition, particularly in *Lactobacillus* and *Acetobacter* species, validated through real-time PCR and 16S sequencing suggesting an adaptive microbial response to pathological stress. Strikingly, microbiome depletion (axenic condition) markedly worsened behavioral and physiological outcomes, including disrupted sleep-circadian rhythms, impaired memory, and reduced locomotor function. These deficits were accompanied by significant increase in neuroinflammatory signaling cascade genes (*Upd3-Dome-Hop-Stat92e*), and apoptotic gene (*Hid* and *Reaper*) expression. Further we found increased lipid spot staining which suggests possible lipid dysregulation, and we also observed a reduced synapsin protein level. Moreover, microbiome loss induced energy stress condition showed marked elevation in phospho-AMPK (p-AMPK) yet failed to restore proteostasis. It is supported by significant increase in the accumulation of ubiquitinated proteins and the autophagy adaptor Ref2p/p62, indicating impaired autophagic flux. Further this dysfunction correlated with increased tau, phospho-tau, and a*β*42 accumulation. Together, our findings demonstrate that microbiome depletion exacerbates glial-mediated inflammation, disrupts circadian and metabolic homeostasis, impairs, and accelerates cognitive and motor decline. This work highlights a previously underappreciated influence of gut and brain microbiome on restraining glial dysfunction and mitigating AD-like pathology, positioning microbial homeostasis as a critical modulator of neurodegenerative disease progression.

Disclosures: K. Madamanchi: None. **S. Reddy:** None. **J. Watson:** None. **G. Melkani:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.06

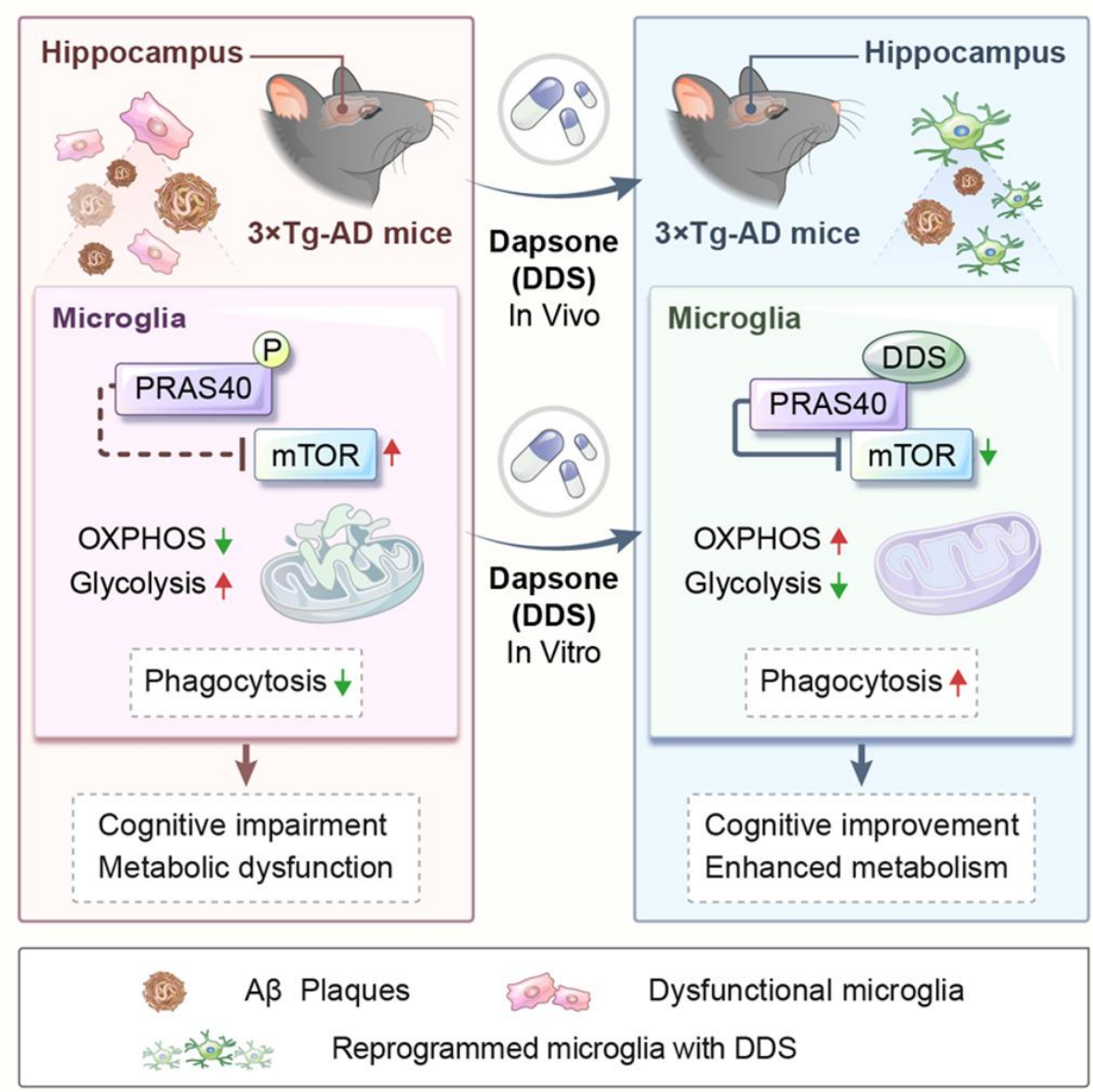
Topic:

Support: National Programs for Brain Science and Brain-like Intelligence Technology of China(STI2030-Major Projects, 2021ZD0200800)
National Natural Science Foundation of China (no. 82288101, no. 82371499)

Title: Restoring metabolism of microglia by dapsone rescues pathology and improves memory in a mouse model of Alzheimer's disease

Authors: K. YUAN[1], ***S. FENG**[2], L. LU[1];
[1]Peking Univ. Sixth Hosp., Beijing, China; [2]Peking university, Beijing, China

Abstract: Background Alzheimer's disease (AD) is characterized by progressive cognitive decline and neuropathological changes, with increasing evidence linking disease progression to altered neuroimmune metabolism. Dapsone (DDS), a clinically approved anti-leprosy drug with reported neuroimmune effects, has not been systematically evaluated in AD. **Methods** The effects of DDS were examined in 3×Tg-AD mice after six weeks of oral treatment using behavioral, pathological, electrophysiological, metabolic, single-cell transcriptomic, chemical proteomic, and microglia-specific genetic analyses. **Results** DDS improved cognitive performance and reduced AD-related pathology in 3×Tg-AD mice. At the cellular level, DDS enhanced microglial phagocytosis of Aβ and synaptosomes and was associated with a metabolic shift from glycolysis toward mitochondrial oxidative phosphorylation. scRNA-seq further showed changes in microglial state composition, with increased homeostatic and proteostasis-associated microglial states and reduced inflammatory microglia. Proline-rich Akt substrate of 40 kDa (PRAS40) was identified as a candidate DDS-interacting protein. DDS treatment was associated with reduced PRAS40-mTORC1 downstream signaling, increased autophagy-related markers, improved mitochondrial function, and altered hippocampal glucose metabolism. Microglia-specific PRAS40 overexpression attenuated the cognitive and pathological effects of DDS, whereas PRAS40 knockdown produced DDS-like effects. **Conclusions** DDS alleviated AD-related cognitive and pathological deficits in 3×Tg-AD mice, accompanied by changes in microglial metabolism, autophagy-related signaling, and microglial state composition. These data support a role for microglial PRAS40-mTORC1 signaling in DDS-associated effects and suggest that microglial metabolic regulation may provide a therapeutic approach for AD.



Disclosures: K. Yuan: None. **S. Feng:** None. **L. Lu:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.07

Topic: B.09. Glial Mechanisms

Support: NIH Grants R01NS117372

Title: Fingolimod Restores Synaptic Function and Modulates Microglial Epigenetic Signaling in a Mouse Model of Alzheimer's Disease

Authors: *G. Y. WILLIAMS[1], Y. XIE[1], Y. CAI[1], L. CHEN[1], H.-Y. CHU[1,2], M. P. BURNS[2,3], S. VICINI[1,2], T. WANG[1,2];
[1]Pharmacol. and Physiol., [2]Interdisciplinary Program in Neurosci., [3]Neurosci., Georgetown Univ., Washington, DC

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia. Although current FDA-approved therapies may slow disease progression, there remains no cure. Synaptic dysfunction is a key driver of cognitive decline in AD, and growing evidence suggests that abnormal epigenetic regulation contributes to disease progression. Recent studies have also implicated sphingosine signaling in synapse stabilization through homeostatic plasticity and epigenetic mechanisms in AD models. Sphingosine, a bioactive lipid involved in multiple cellular processes, is reduced in postmortem AD brain tissue. Fingolimod, also known as FTY720, is an FDA-approved sphingosine analog used to treat relapsing multiple sclerosis. Although it primarily acts as an immunomodulatory drug in the periphery, FTY720 has also been shown to exert neuroprotective effects in the central nervous system. Here, we investigated whether FTY720 rescues behavioral, synaptic, and glial deficits in the 5XFAD mouse model of familial AD. Behavioral experiments showed that FTY720 treatment improved motor function, restored associative memory, and enhanced spatial memory in 5XFAD mice. Whole-cell patch-clamp recordings further revealed that FTY720 rescued excitatory and inhibitory synaptic function in hippocampal CA1 pyramidal neurons. Immunohistochemistry and confocal imaging demonstrated that FTY720 preserved dendritic spine density without altering the overall dendritic morphology of CA1 pyramidal neurons. Notably, FTY720 also increased microglial cell density and altered microglial morphology and process motility in AD mice. In addition, FTY720 rescued the AD-associated reduction in microglial H3K9 acetylation (H3K9ac), suggesting that its beneficial effects may involve epigenetic regulation within microglia. Together, these findings indicate that FTY720 improves cognitive and behavioral outcomes in AD mice by restoring synaptic function and modulating microglial epigenetic signaling. These results highlight sphingosine-based signaling as a promising therapeutic pathway for targeting synaptic dysfunction and glia-neuron interactions in Alzheimer's disease.

Disclosures: G.Y. Williams: None. **Y. Xie:** None. **Y. Cai:** None. **L. Chen:** None. **H. Chu:** None. **M.P. Burns:** None. **S. Vicini:** None. **T. Wang:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.08

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

Support: NSFC 82104416
NSFC 82571613

Title: Membralin Regulates Microglial Store-Operated Ca^{2+} Entry and Neuroinflammation in Alzheimer's Disease

Authors: *Y. LIU, Y. ZHANG;
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Abstract: Alzheimer's disease (AD) remains therapeutically challenging due to its complex pathogenesis, with Ca^{2+} dyshomeostasis as a central driver of disease progression. Increasing evidence implicates microglial dysfunction in AD pathogenesis, yet the molecular mechanisms linking disrupted Ca^{2+} signaling to neuroinflammation remain poorly understood. Store-operated Ca^{2+} entry (SOCE), a key regulator of immune responses in non-excitable cells, represents a potential mechanistic link. However, how SOCE is regulated in microglia and whether it contributes to neurodegeneration remain largely unknown.Here, we identify Membralin, an endoplasmic reticulum (ER)-resident transmembrane protein implicated in ER-associated degradation, as a novel regulator of SOCE. In both CRISPR/Cas9-mediated Membralin knockout (KO) HEK293T cells and Membralin KO primary microglia, we observed a significant increase in SOCE-mediated Ca^{2+} influx ($p<0.01$). Among SOCE pathway components, Membralin deficiency selectively increased STIM2 protein expression ($p<0.05$) without affecting STIM1 levels. Co-immunoprecipitation and FRET analyses demonstrated direct interactions between Membralin and both STIM1 and STIM2. Domain mapping revealed that the N-terminus of Membralin interacts with STIM1, and the CC1-SOAR domains—critical for STIM activation and oligomerization—mediate this interaction, identifying Membralin as a key SOCE regulator. Biotinylation assays showed increased membrane-associated STIM1 in Membralin KO cells, whereas degradation and imaging assays showed that Membralin promotes STIM2 clustering and degradation, but not STIM1. Following the elevated SOCE activity, NFAT nuclear translocation was increased in Membralin KO cells, leading to upregulation of downstream pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β ($p<0.05$). Given the role of Ca^{2+} dyshomeostasis in AD, we examined STIM expression in human AD brain tissue and found increased STIM1 and STIM2 levels in both sexes ($p<0.05$ vs. controls). Similar results were observed in the hippocampus of 5xFAD mice. Furthermore, in the microglia-specific Membralin deletion mice (*Membralin*$^{f/f}$;*Cx3cr1-Cre*) , the hippocampal synaptic transmission input-output and long-term potentiation were enhanced. Together, these findings identify Membralin as a previously unrecognized checkpoint linking ER protein quality control to microglial SOCE. By coordinating STIM1 retention and STIM2 degradation, Membralin integrates calcium homeostasis, neuroinflammatory signaling, and synaptic dysfunction, highlighting a potential therapeutic strategy for Alzheimer's disease.

Disclosures: Y. Liu: None. **Y. Zhang:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.09

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

Support: NIH Grant R01AG073292
Cure Alzheimer's Fund
Coins for Alzheimer's Research Trust Fund
Freedom Together Foundation
BrightFocus Foundation

Title: TREM2 Mutations as a Lens on Microglial Dysfunction & Considerations for Innate Immune Targets

Authors: D. J. PILAT[1], H. LE[1], D. PROKOPENKO[1], C.-C. LIN[1], W. EIMER[1], L. QUINTI[1], E. P. GAVRILLES[1], R. I. SADREYEV[2], R. E. TANZI[1], ***A. GRICIUC**[1];
[1]Neurol., [2]Mol. Biol., Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA

Abstract: Genetic studies of Alzheimer's disease (AD) have revealed *TREM2* among dozens of AD-associated genes involved with microglial function. TREM2, an innate immune receptor, regulates microglial activation, phagocytosis, and biosynthetic metabolism in AD. Our prior work established that the T96K mutation in *TREM2* confers a gain-of-function *in vitro*, based on its ability to increase ligand-dependent activation. Most recently, we showed that the gain-of-function mutation, $TREM2^{T96K}$ is associated with increased risk for AD using a whole-genome sequencing dataset comprised of both family-based and case-control samples. To investigate the effects of a *TREM2* gain-of-function mutation in AD, we generated a novel $Trem2^{T96K}$ knockin mouse model. We show that $Trem2^{T96K}$ markedly reduces the capacity of microglia to encase amyloid beta (Aβ) plaques, decreases levels of soluble Trem2, and impairs the transition of homeostatic microglia into disease-associated microglia (DAM), specifically, in female *5xFAD* mice. We also observed lower levels of soluble Trem2 and impaired uptake of Aβ in $Trem2^{T96K}$ knockin microglial cells. Single-cell RNA sequencing revealed concomitant suppression of DAM gene signature, activation of homeostatic genes, and defects in microglial trajectories from homeostatic state into DAM. Thus, we show that like the loss-of-function mutation R47H, a gain-of-function *TREM2* mutation (T96K) also leads to impaired microglial function in a sex-dependent manner. Since *TREM2* is currently one of the most targeted AD genes in the pharmaceutical industry, our findings should facilitate the development of TREM2-targeted therapies for the prevention and treatment of AD. Insights from *TREM2* mutation-specific mechanisms with high translational potential should help guide on how innate immune targets can be evaluated against complex microglial phenotypes and disease-specific gene signatures.

Disclosures: D.J. Pilat: None. **H. Le:** None. **D. Prokopenko:** None. **C. Lin:** None. **W. Eimer:** None. **L. Quinti:** None. **E.P. Gavrilles:** None. **R.I. Sadreyev:** None. **R.E. Tanzi:** None. **A. Griciuc:** None.

Nanosymposium

NANO08: Neural-Immune Signaling in Alzheimer's Disease

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO08.10

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

Title: Plaque-associated oligodendrocyte proteostatic failure is linked to myelin loss in Alzheimer’s disease

Authors: *J. SHIN;
Data, AI, and Genome Sci. (DAGS), Merck Res. Labs., Cambridge, MA

Abstract: Alzheimer’s disease (AD) features amyloid-β plaques and tau pathology, yet early and clinically significant myelin loss remains mechanistically unresolved. Here, we report human iPSC-derived forebrain organoids with doxycycline-inducible expression of SOX10, OLIG2, and NKX6-2 (SON) that generate robust, mature oligodendrocytes and compact myelin in vitro and in vivo. Introducing amyloid precursor protein (APP) pathogenic mutations produces extracellular amyloid-β plaques and phosphorylated tau with reduced myelin basic protein (MBP) expression and disrupted myelin ultrastructure. Single-cell and spatial transcriptomics combined with amyloid plaque imaging reveal a plaque density-dependent oligodendrocyte transcriptional reprogramming, coordinately inducing immune activation, calcium signaling, lipid remodeling, and proteasomal subunit remodeling, that is incompatible with MBP protein accumulation. This program is conserved in human AD spatial transcriptomics, implicating proteostatic disruption as a mechanism underlying the transcript-protein disconnect and myelin loss in AD.

Disclosures: J. Shin: None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO09.01

Topic: D.03. Stroke

Support: NIH Grant T32DC019481
NIH Grant R01HD105735
NIH Grant NCATS KL2 TR001432

Title: Lateralization of visuospatial processing following right hemisphere stroke

Authors: *K. WEGNER-CLEMENS, M. BOLDEN, K. SHATTUCK, A. SEYDELL-GREENWALD;
Georgetown Univ., Washington, DC

Abstract: Visual spatial processing has previously been shown to be lateralized to the right hemisphere. Participants with right hemisphere lesions often exhibit deficits in spatial attention, such as hemispatial neglect, where participants fail to attend to visual information on the left side despite not having a visual deficit on the right side. Similarly, in the classic Landmark Task, participants are asked to judge if a line has been bisected at the middle or not. Compared to people without lesions or with left-hemisphere lesions, people with right hemisphere lesions are more likely to bisect the line to the right of the true midpoint. When healthy adults with no visuospatial deficits complete the Landmark Task during an fMRI scan, the right parietal cortex is preferentially activated, adding further support for right lateralization of visual spatial processing prior to stroke. However, it has not previously been investigated if visual spatial processing remains right lateralized following stroke. Prior studies have shown that in individuals with left-hemisphere stroke, language activation, which is typically left lateralized, is reduced in the left hemisphere but slightly increased in homotopic regions of the right hemisphere. In analogy, we hypothesized that in individuals with right-hemisphere stroke, we might observe reduced right and increased left parietal activation. To test this hypothesis, we recorded functional MRI data from right hemisphere stroke survivors tested >1 year post-stroke (N=22) and neurologically healthy adults (N=11) while they completed a line bisection judgement and line luminance judgment control task, and activation between groups for spherical ROI around peak activation in anatomically defined parietal regions of interest (left and right BA40). For the contrast between the line bisection and luminance judgement, there was a reduction of right parietal activation for the RH stroke group relative to controls, but this reduction was not statistically significant (uncorrected p=0.17). However, contrary to the hypothesis of increased contralateral activation, the right hemisphere stroke group also showed less activation than controls in the left parietal lobe (uncorrected p=0.004). These results suggest that there is no compensatory left parietal activation for visual spatial processing following right hemisphere stroke.

Disclosures: K. Wegner-Clemens: None. **K. Shattuck:** None. **A. Seydell-Greenwald:** None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO09.02

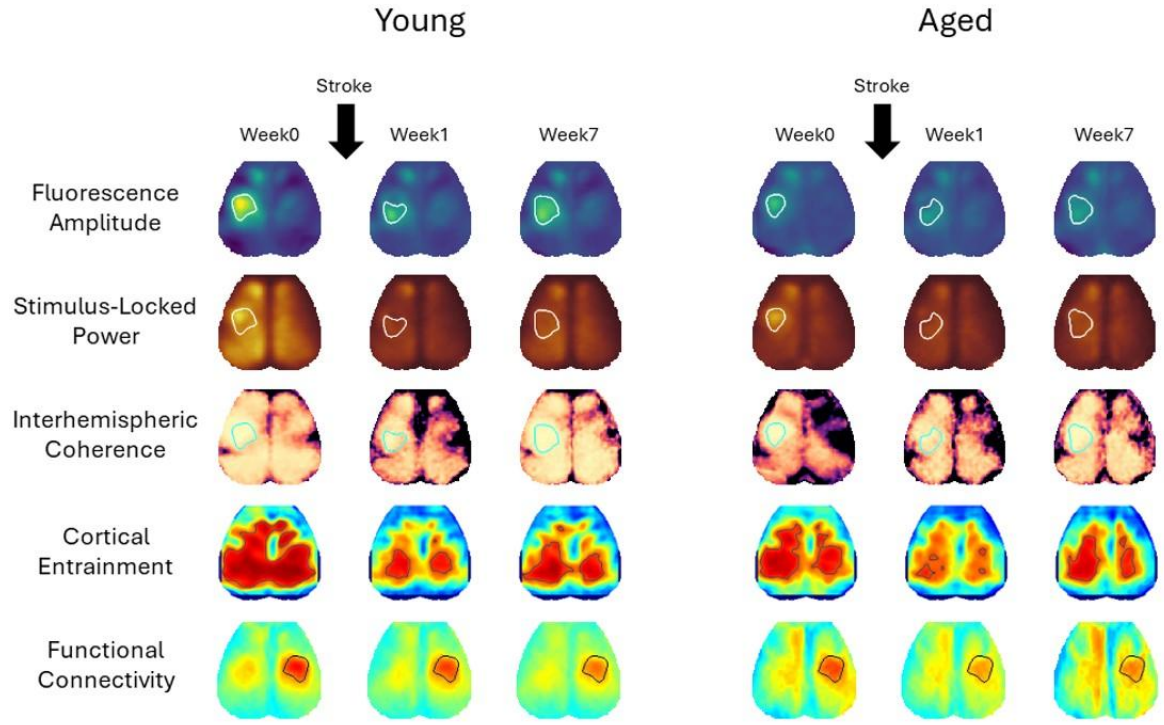
Topic: D.03. Stroke

Support: K08NS117888

Title: Normal Aging Limits Cortical Network Reorganization and Behavioral Recovery after Experimental Stroke

Authors: *R. M. BOWEN[1], A. ALBERTSON[1], A. Q. BAUER[2], J.-M. LEE[1];
[1]Neurol., [2]Radiology, Washington Univ. in St. Louis, St. Louis, MO

Abstract: Stroke is the leading cause of chronic disability in the United States, and advancing age is associated with worse recovery. Yet relatively little is known about how aging influences the repair and reorganization of neural circuits and large-scale cortical networks after stroke. We used wide-field calcium imaging to compare cortical network dynamics and behavioral recovery after focal photothrombotic stroke in forepaw somatosensory cortex in young (3-month-old) and aged (18-month-old) Thy1-GCaMP6f mice. Both young and aged mice developed significant somatomotor deficits after stroke, but only young mice exhibited substantial behavioral recovery despite similar infarct volumes across groups. While young and aged mice showed differences in baseline forepaw-evoked response amplitudes and their trajectories after stroke, the temporal dynamics of these circuits were comparable between young and aged mice both before and after stroke, suggesting a degree of resilience of local neuronal circuits. Neuronal network dynamics proved to be a more sensitive measure of age- and stroke-related degradation. Young mice demonstrated more coordinated neuronal network dynamics at baseline, as measured by hemispheric stimulus-locked fidelity, bilateral coherence, and cortical entrainment, that were significantly disrupted after stroke and did not recover after 7 weeks; aged mice exhibited disorganized network dynamics at baseline and no significant changes after stroke. Reductions in the spatial extent of cortical entrainment between baseline and 1-week post-stroke predicted long-term behavioral recovery across animals and groups. Finally, only young mice showed significant recovery of somatosensory and somatomotor functional connectivity by 7 weeks after stroke. These results suggest similarities in neuronal network degradation caused by aging and stroke and highlight the vulnerability of neuronal networks, relative to local neuronal circuits, in both processes. Our findings also indicate a potential network-level basis for chronic deficits in stroke survivors.



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Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO09.03

Topic: C.01. Brain Wellness and Aging

Support: DBT/RLF/Re-Entry/23/2022
ANRF/ECRG/2025/002540/LS

Title: Inositol Pyrophosphate Signaling in Neurodegeneration

Authors: *L. NAGPAL;
Univ. of Calcutta, Kolkata, India

Abstract: Ischemic stroke remains a leading cause of death and long-term neurological disability worldwide. Despite advances in acute clinical management, effective therapies that promote sustained neuroprotection and functional recovery remain limited. Growing evidence suggests that dysregulated cellular stress responses, oxidative damage, and mitochondrial dysfunction are key contributors to neuronal loss following ischemic injury. Understanding the molecular mechanisms that govern these processes is therefore essential for the development of novel therapeutic strategies. In this study, we investigated the role of inositol pyrophosphate signaling in the regulation of neuronal homeostasis and stress adaptation. Proteomic analysis of mouse brain tissue identified a network of proteins associated with a key enzyme involved in inositol pyrophosphate synthesis. These interacting partners were predominantly linked to antioxidant defense, mitochondrial protein quality control, and cellular stress-response pathways, suggesting a broader role for this signaling axis in maintaining neuronal integrity. Biochemical validation confirmed the association of the identified proteins with the signaling enzyme, supporting the existence of a functional protein complex in the brain. Further analyses using gene-deficient mouse models revealed significant alterations in the expression of proteins involved in redox regulation and mitochondrial stress responses. Loss of the enzyme was associated with reduced antioxidant capacity and compensatory changes in mitochondrial protective mechanisms, indicating disruption of cellular homeostasis. These findings suggest that inositol pyrophosphate signaling plays a critical role in coordinating oxidative stress responses and maintaining mitochondrial function under physiological conditions. Collectively, our results reveal a previously underappreciated link between inositol pyrophosphate metabolism, redox balance, and mitochondrial proteostasis in the brain. Given the central roles of oxidative stress and mitochondrial dysfunction in ischemic injury and neurodegenerative disorders, these findings provide important mechanistic insights into pathways that may influence neuronal vulnerability and recovery. This work highlights the potential of targeting inositol pyrophosphate-mediated signaling networks as a promising strategy for neuroprotection and improved neurological outcomes following stroke and related brain disorders.

Disclosures: L. Nagpal: None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

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Time: Sunday, November 15, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO09.04

Topic: D.03. Stroke

Support: NIH R21 NS131754-01A1
Supported by Univ. of Pittsburgh Department of Neurology Start-up funding

Title: Astrocytic NBCe1 Deficiency Promotes Metabolic Reprogramming and Reduces Ischemic Brain Injury

Authors: *G. BEGUM[1,2,3], O. CAPUK[2], Q. KONG[4], E. BERTHOLD[2], K. KALIYAPPAN[2], R. MUDUGANTI[2], V. FIESLER[2,3], D. RAJASUNDARAM[5], G. KOHANBASH[4,6], S. GADANI[2]; [1]Neurol., [2]Neurology, Pittsburgh Inst. for Neurodegenerative Dis., [3]Veterans Affairs Res. Ctr., [4]Neurolog. Surgery, [5]Pediatrics, Div. of Hlth. Informatics, UPMC Children's Hosp., [6]Immunol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Astrocytes play a key role in maintaining brain energy metabolism and homeostasis by supporting neuronal function through glucose, amino acid and lipid metabolism. Astrocyte dysfunction following ischemic stroke disrupts metabolic balance, alters glycolytic flux and mitochondrial function, and promotes chronic inflammation. In this study, we investigated the role of astrocytic electrogenic sodium bicarbonate transporter-1 (NBCe1) in stroke induced brain damage. NBCe1 is predominantly expressed in astrocytes and plays important role in brain pH homeostasis. Increased NBCe1 expression in astrocytes correlates with neurological impairment in ischemic stroke and the mechanisms remain unclear. Our study utilized tamoxifen inducible *Gfap-Cre*$^{ERT2+/-}$*;Nbce1*$^{f/f}$ mice to selectively delete *Nbce1* in GFAP^{+} reactive astrocytes. Mice deficient in NBCe1 in astrocytes (*Nbce1* cKO) displayed reduced infarct volume, neuronal loss and neurological function impairment at 1-5-day after stroke (transient middle cerebral occlusion model, tMCAO). Cytokine array analysis of wild-type (WT) and *Nbce1* cKO ischemic brain hemispheres revealed elevated anti-inflammatory mediators in *Nbce1* cKO ischemic brains compared to the WT controls. Single cell RNA sequencing (Sc-RNAseq) further demonstrated profound transcriptomic reprogramming in astrocytes from *Nbce1* cKO stroke brains. These astrocytes exhibited enhanced oxidative phosphorylation (OxPhos), increased cholesterol metabolism, and strengthened antioxidant defenses, including upregulation of mitochondrial complex I and cholesterol biosynthesis genes. In addition, microglia/macrophage (M/MΦ) clusters from *Nbce1* cKO stroke brains displayed a distinctly immunomodulatory, anti-inflammatory transcriptional profile, with IL-10 among the most significantly upregulated genes. We propose that pathological activation of NBCe1 increases Na^{+} influx and intracellular alkalinization, leading to impaired mitochondrial function, metabolic stress, increased reactive oxygen species production, and activation of inflammatory signaling. Together, our findings

indicate that astrocyte specific deletion of *Nbce1* restores metabolic homeostasis, dampens inflammatory signaling, and promotes a neuroprotective environment following ischemic stroke.

Disclosures: G. Begum: None. **O. Capuk:** None. **Q. Kong:** None. **E. Berthold:** None. **K. Kaliyappan:** None. **R. Muduganti:** None. **V. Fiesler:** None. **D. Rajasundaram:** None. **G. Kohanbash:** None. **S. Gadani:** None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO09.05

Topic: D.03. Stroke

Title: Post-Stroke Cognitive-Affective Impairment in Middle-Aged Acyclic Rats is Attenuated by Ovariectomy

Authors: *K. A. PICKLE[1], S. BAKE[2], R. JARAMILLO[3], N. SHRESTHA[3], M. SAATHOFF[3], A. EVANS[3], F. SOHRABJI[2];
[1]Texas A&M Univ. Col. of Med., Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Univ. Syst. Hlth. Scien, Bryan, TX; [3]Texas A&M Univ., College Station, TX

Abstract: POST-STROKE COGNITIVE-AFFECTIVE IMPAIRMENT IN MIDDLE-AGED ACYCLIC RATS IS ATTENUATED BY OVARIECTOMYPickle KA, Bake S, Jaramillo R, Shrestha N, Saathoff M, Evans A, Sohrabji F Department of Neuroscience and Experimental Therapeutics, Women's Health in Neuroscience Program, Texas A&M College of Medicine, Bryan, TX.
After menopause, women have higher stroke incidence and severity, coinciding with ovarian hormone loss. We model menopause with reproductively senescent (RS; ≥10mos), acyclic female Sprague Dawley rats that have low progesterone, undetectable estradiol, and elevated FSH. Our lab has shown normally cycling adult females (5-7mos) sustain smaller infarcts after middle cerebral artery occlusion (MCAo) than RS rats. Ovariectomy (OVX) in adults increases infarct volume, paradoxically, in RS rats it reduces infarct volume and sensorimotor deficits. This study determined if the benefits of OVX in RS females on acute stroke effects persist in the chronic phase. RS rats received OVX or sham surgery and underwent MCAo or sham surgery 3 weeks later. At 30d post-stroke we assessed affective/cognitive behaviors (Burrowing, Social Interaction, NORT, Barnes maze). Ovary intact rats spent less time in the social chamber after stroke. NORT, which tests episodic memory, showed no significant differences, but intact groups favored the familiar object while OVX rats favored the novel. In the Barnes maze test, which test hippocampal spatial learning and recall, ovary-intact rats failed to improve latency in the learning phase, while OVX rats had decreased latency and greater use of hippocampal strategies. Overall, RS OVX rats display better hippocampal learning and social motivation. At termination, spleens were larger and serum Insulin-like Growth Factor (IGF)-1, a stroke neuroprotectant, was elevated in stroke OVX rats. When combined with our previous studies, these results show the

aging ovary shapes acute immunity which persists in the chronic phase altering stroke recovery. These data support the hypothesis that the aging ovary may act as an immune organ that is deleterious to stroke recovery.

Disclosures: K.A. Pickle: None. **S. Bake:** None. **R. Jaramillo:** None. **N. Shrestha:** None. **M. Saathoff:** None. **A. Evans:** None. **F. Sohrabji:** None.

Nanosymposium

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Presentation Number: NANO09.06

Topic: D.03. Stroke

Support: Merit Review Award Number 1I01BX006223-01A1 from the U.S. Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service
Merit Review Award Number I01 RX003506 from the U.S. Department of Veterans Affairs Rehabilitation R&D (RR&D) Service
Florida Department of Health #25K06
American Heart Association (AHA; 25TPA1476464)

Title: Estrogen receptor-beta activation improves post-stroke cognition in reproductively senescent female rats

Authors: *F. R. DESAI[1], I. CABEDA DIAZ[1], A. P. RAVAL[1,2,3];
[1]Neurol., [2]Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL;
[3]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL

Abstract: Chronic 17β-estradiol (E2) treatment is neuroprotective in experimental brain injury models; however, its clinical translation has been limited by safety concerns. Our previous studies demonstrated that pre- and post-ischemic activation of estrogen receptor-β (ER-β) reduces both ischemic brain injury and cognitive deficits in female rats [1, 2]. The present study investigated the neuroprotective effects of post-stroke ER-β activation in reproductively senescent (RS) female rats. Retired breeder Sprague-Dawley rats were classified as RS after remaining in constant diestrus for >1 month. Animals underwent transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery and were randomized to receive either the ER-β agonist diarylpropionitrile (DPN; 1 mg/kg, s.c.) or vehicle, beginning 4.5 h after tMCAO and every 48 h thereafter for 21 days. Forty-eight hours after the final treatment, infarct volume was assessed histologically. A separate cohort underwent Morris Water Maze testing beginning 18 days after tMCAO to evaluate hippocampal-dependent learning, memory, and working memory. Results demonstrated that DPN treatment significantly reduced infarct volume compared with vehicle-treated and untreated tMCAO groups (20.1 ± 4.3 mm³ vs. 48.5 ± 5.3 mm³ and 60.8 ± 4.8 mm³, respectively; $p < 0.05$). Vehicle treatment did not alter infarct volume compared with tMCAO alone. In behavioral testing, DPN-treated rats exhibited significantly shorter escape

latencies during acquisition training, indicating improved spatial learning. During the probe trial, DPN-treated animals spent significantly more time in the target quadrant, reflecting enhanced memory retention. In working memory testing, DPN-treated rats located the relocated platform significantly faster than vehicle-treated animals, indicating the ER-β activation enhanced post-tMCAO working memory performance. Our findings demonstrate that periodic ER-β activation after stroke reduces ischemic brain damage and improves cognitive recovery in RS female rats, supporting ER-β as a promising therapeutic target for post-stroke recovery in aging females.

Disclosures: F.R. Desai: None. **I. Cabeda Diaz:** None. **A.P. Raval:** None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

Location: WCC Rm 140

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Presentation Number: NANO09.07

Topic: D.03. Stroke

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American Heart Association (AHA; 25TPA1476464)
American Heart Association (AHA; 26PRE1368728)

Title: Irisin therapy improves cognitive recovery after chronic ischemic stroke

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Abstract: Stroke is a leading cause of long-term disability, with persistent cognitive impairment remaining a major barrier to recovery. We previously demonstrated that whole-body low-frequency vibration (LFV; 40 Hz), a non-invasive exercise-mimetic therapy, enhances motor and cognitive recovery after transient middle cerebral artery occlusion (tMCAO) and elevates circulating levels of the neuroprotective myokine irisin [1,2]. Furthermore, post-stroke irisin treatment improves functional outcomes in middle-aged rats [3]. Based on these findings, we investigated the therapeutic potential of irisin for promoting recovery during the chronic phase of stroke. We hypothesize that delayed irisin therapy, initiated one month after stroke, improves spatial learning and memory in middle-aged female rats. Middle-aged Sprague-Dawley rats underwent tMCAO (90 min) to model a stroke. Rats that survived to 4 weeks post-tMCAO were randomized to receive either recombinant irisin (0.2 μg/g BW; IP) or saline once weekly during weeks 5-8 post-tMCAO. Spatial learning and memory were assessed using the Morris water

maze during weeks 7-8. During acquisition testing, rats treated with irisin showed improved performance compared with saline treated rats. Specifically, on Day 4 of testing, the tMCAO + irisin group had significantly reduced latency to locate the hidden platform compared with the tMCAO + saline group ($p<0.05$), suggesting improved spatial learning. The improvement in spatial learning was not attributable to differences in gross motor performance, as swimming velocity (saline: 26.58 ± 6.22 cm/s; irisin: 21.73 ± 9.67 cm/s; $p=0.5420$) and path length (saline: 348.76 ± 168.64 cm; irisin: 410.05 ± 139.58 cm; $p=0.6812$) were not significantly different across groups on Day 4. During the probe trial on Day 5, irisin-treated stroke rats spent significantly more time in the goal quadrant compared with saline-treated stroke rats, indicating enhanced spatial memory capabilities. Together, our findings suggest that delayed irisin therapy improves cognitive recovery in a chronic stroke model, even when treatment is initiated one month after stroke.References:1. Kerr et al. (2022). Post-stroke low-frequency whole-body vibration improves cognition in middle-aged rats of both sexes. Front. aging neurosci, 14, 942717.2. Raval et al. (2018). Whole Body Vibration Therapy after Ischemia Reduces Brain Damage in Reproductively Senescent Female Rats. IJMS, 19(9), 2749.3. Patel et al. (2026). Recombinant Irisin Therapy Alters Brain Transcriptome and Protects Against Ischemic Damage in Middle-Aged Rats. Stroke, 57(1), 197-204.

Disclosures: S.H. Patel: None. **I. Cabeda Diaz:** None. **H.M. Bramlett:** None. **A.P. Raval:** None.

Nanosymposium

NANO09: Stroke: Mechanisms of Abnormal Function and Neurorestorative Strategies

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Topic: D.03. Stroke

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Title: Hemodynamic and electrophysiological progression of the Rose Bengal photothrombotic stroke model in mice

Authors: P. CHARY[1], S. DAVIDSON[2], S. REHMANI[2], X. LI[5], S. CHEN[3], ***G. SILASI**[4]; [1]Univ. of Ottawa, Ottawa, ON, ; [2]Cell. and Mol. Med., [3]Dept. of Cell. and Mol. Med., [4]Univ. of Ottawa, Ottawa, ON, Canada; [5]Ottawa university, Ottawa, ON.

Abstract: The photothrombotic stroke model is gaining popularity due to its relative simplicity, minimal invasiveness, and clinical relevance. Photothrombosis involves the delivery of an intravascular photosensitizer (Rose Bengal) followed by its photoactivation, resulting in vessel occlusion and ischemia. Using a combination of complementary optical and nonoptical techniques, we characterized the physiological changes in mice undergoing photothrombosis. We

report that Rose Bengal has vasoconstrictive properties, inducing hypoemia both in the brain and periphery even in the absence of its photoactivation. Conversely, we find that light, when used at photothrombosis-appropriate intensities and durations, induces large amounts of tissue heating and hyperemia even in the distal nonilluminated hemisphere. Furthermore, we show that use of the optimal photothrombotic wavelength based on the Rose Bengal absorption spectrum (yellow-561nm) produces a more consistent and pronounced drop in blood flow, and a shorter latency to the initial spreading depolarization (SD), ultimately resulting in a larger stroke. Similarly, when yellow light is used to induce a stroke in ChR2-expressing mice, the electrophysiological and hemodynamic confounds from green light cross-activation of ChR2 are eliminated. Finally, we observe across cohorts that male mice have larger strokes than females. Altogether, we extensively describe important caveats and confounds concerning photothrombosis and provide a detailed characterization of its early ischemic events.

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Nanosymposium

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Topic: D.03. Stroke

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Title: Neuroprotective Roles of Sulfonylurea Receptor 1 and Epac2 Inhibition in Hemorrhagic and Ischemic Stroke Models

Authors: *T. IGARASHI, M. KOBAYASHI, R. KAJIMOTO, K. SHIJO, A. YOSHINO; Dept. of Neurolog. Surgery, Nihon Univ. school of Med., Tokyo, Japan

Abstract: Secondary brain injury (SBI) following stroke, including subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and cerebral infarction (CI), significantly impacts functional outcomes. Sulfonylurea receptor 1 (SUR1) and exchange protein directly activated by cAMP 2 (Epac2) are critical mediators of edema and cell death in SBI, yet their integrated roles across different stroke types require clarification. We evaluated the therapeutic potential of targeting these pathways using adult male Sprague-Dawley and Wistar rats (237-388 g, n=6-11 per group). Sex differences were not assessed. Models included SAH (endovascular puncture), ICH (collagenase injection), and CI (middle cerebral artery occlusion). To target SUR1, glibenclamide was administered via osmotic pumps. To inhibit Epac2, ESI-05 was administered intraperitoneally (8 mg/kg). All experimental assessments were performed in a blinded manner. Assessments included brain water content (dry-wet method), microglial activation (Iba1, Galectin-3), and apoptotic signaling (p38-MAPK, cleaved caspase 3). Results showed that ABCC8 (SUR1 mRNA) and Epac2 were significantly upregulated in peri-lesional areas across

models. In SAH, glibenclamide reduced brain water content (90±19% vs 69±9% in controls, $p<0.001$; one-way ANOVA/Tukey) and suppressed microglial activation and pro-inflammatory cytokines (IL-1β, TNFα). In ICH, glibenclamide significantly reduced water content ($p=0.008$) and expression of Galectin-3 and CD11b on the injury side. In CI, glibenclamide reduced swelling (10±4% vs 28±7% in controls, $p<0.01$) and hemorrhagic transformation. Epac2 inhibition via ESI-05 reduced infarct volume (65.3±2.5% vs 72.9±2.1% in controls, $p<0.05$; unpaired t-test) and water content ($p<0.05$). This neuroprotection was mediated by attenuation of the p38-MAPK/caspase 3 signaling pathway, leading to improved neurological scores ($p<0.001$; Mann-Whitney U-test). Our findings demonstrate that SUR1 and Epac2 are pivotal in the pathophysiology of SBI. Targeted inhibition represents a promising strategy to ameliorate edema and neuroinflammation, potentially improving clinical outcomes for diverse stroke patients.

Disclosures: T. Igarashi: None. **M. Kobayashi:** None. **R. Kajimoto:** None. **K. Shijo:** None. **A. Yoshino:** None.

Nanosymposium

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Topic: I.04. Executive Functions

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Title: Adaptive Processing of Visual and Reward Information during Dynamic Foraging in Visual and Parietal Cortex

Authors: *C. XUE[1], V. HA[2], M. R. COHEN[2];
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Abstract: Primate decision-making in a natural environment requires the flexible integration of sensory salience, reward history, and internal belief states. With simultaneous electrophysiological recordings in macaque visual (V4) and parietal (7a) cortical regions during a dynamic foraging task with bated rewards, we investigate how these variables are represented and contextually modulated in the brain. During this task, monkeys' choices are driven by reward probability and sensory salience. At the neural level, we found that macaque V4 neurons encode the stimulus features of the chosen image more independently and veridically than those of the unchosen image. This reveals a more comprehensively robust processing of information relating to the animal's choice, even when they is not directly related to rewards. To further investigate the circuit mechanisms underlying this integration of image features and reward-seeking behavior, we used computational models to reproduce the monkeys' choice patterns. We found

distinct behavioral states with different focuses on reward value and image salience, with corresponding differences in the representations of these variables in the model. To causally test the hypothesis that these robust neuronal representations drive different behavioral patterns, we collected behavioral and neuronal data after one monkey orally ingested methylphenidate, which is an effective substance against ADHD in humans and has been shown to enhance visual attention in monkeys. As expected, we observed an even more pronounced choice-dependent enhancement in the independent, orthogonal representation of visual features in V4, together with a stronger salience dependence in the behavioral choices. Future research into the neuronal basis of these behavioral states will reveal the critical biological constraints governing how the brain balances exogenous sensory information with goal-directed behavior.

Disclosures: C. Xue: None. **V. Ha:** None. **M.R. Cohen:** None.

Nanosymposium

NANO10: Executive Control of Perception, Action, and Decision-Making

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Presentation Number: NANO10.02

Topic: I.04. Executive Functions

Support: NIH/NEI R01 EY032555
NIH/NEI R01 EY034605
R00 EY025026

Title: Investigating context-dependent interlaminar interactions in the primary visual cortex

Authors: *X. XU[1], M. MORTON[2], S. DENAGAMAGE[2], A. S. NANDY[3], M. P. JADI[4];
[2]Neurosci., [3]Dept. of Neurosci., [4]Dept. of Psychiatry, [1]Yale Univ., New Haven, CT

Abstract: Our visual experience is a result of the concerted activity of neuronal ensembles in the sensory hierarchy. Yet how the spatial organization of objects influences this activity remains poorly understood. We investigate how inter-laminar information flow within the primary visual cortex (V1) is affected by visual stimuli in isolation or with flankers at spatial configurations that are known to cause non-uniform degradation of perception. By employing dimensionality reduction approaches to simultaneous layer-specific population recordings, we establish that information propagation between cortical layers occurs along a structurally stable communication subspace. The spatial configuration of contextual stimuli differentially modulates inter-laminar communication efficacy, the balance of feedforward and effective feedback signaling, and contextual signaling in the superficial layers. Remarkably, these modulations mirror the spatially non-uniform aspects of perceptual degradation. Our results suggest a model of retinotopically non-uniform cortical connectivity in the output layers of V1 that influences information flow in the sensory hierarchy.

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Nanosymposium

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Presentation Number: NANO10.03

Topic: I.04. Executive Functions

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Title: Optotagging interareal projection neurons to study corticocortical communication in macaque visual cortex

Authors: *J. M. HASSE[1], M. O. BOHLEN[2], J. G. KELLY[3], M. J. HAWKEN[3], J. A. MOVSHON[3];
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Abstract: Understanding the communication between cortical areas is fundamental to primate neuroscience. During typical electrophysiological experiments in the macaque brain, we rarely know whether a recorded neuron actually sends its output to a given downstream area. Distinguishing projection neurons from the surrounding population in vivo remains a major barrier to studying interareal communication in the macaque, in part because the genetic and molecular tools that target projection-defined neurons in rodents remain underdeveloped in primates. Optotagging, the use of photoresponses of opsin-expressing neurons to identify them in vivo, offers a path forward, but applying it to excitatory corticocortical pathways requires distinguishing directly labeled projection neurons from their synaptically driven neighbors. We developed an optotagging approach to label and record the V1 neurons that project to V2. We injected AAVretro-ReaChR into V2 of 3 macaques and, after 6-9 mo of expression, recorded photoresponses of V1 neurons under anesthesia using multicontact linear arrays. Of 142 neurons recorded across the depth of surface V1, 49 were significantly photosensitive, falling along a continuum of photoresponse rate and onset latency that reflects varying contributions of direct opsin-mediated photocurrents and indirect synaptic currents. To order this continuum, we measured the trial-to-trial reliability of spike timing in the photoresponse, validated against rat experiments in which synaptic activity was pharmacologically silenced. Reliability separated the population more effectively than light-evoked latency or firing rate, grading from a high-reliability extreme whose photoresponses resembled direct current injection, through neurons with mixed direct and indirect input, to a low-reliability extreme likely dominated by synaptic currents. Rather than impose hard boundaries on this graded distribution, we applied a conservative reliability threshold to identify the neurons most confidently driven directly. Nineteen of 49 photoresponsive neurons met the high-reliability criterion and were classified as optotagged (13%, 19/142). This approach enables the study of a defined output channel and how it contributes to interareal signaling through the recording of the interareal projection neurons and the surrounding local population simultaneously. Optotagging is an effective tool for

dissecting corticocortical communication in the macaque, and will become more powerful as genetic and molecular tools continue to improve.

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Nanosymposium

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Topic: I.04. Executive Functions

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Title: Coordinated Activity Within and Across Visual and Parietal Areas Aligns Visual Representations with Behavior

Authors: *R. SRINATH[1], M. R. COHEN[2];
[2]Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: Adaptive behavior requires the brain to flexibly map the same visual input onto different actions depending on current goals. In monkey visual cortex, neurons in area V4 are modulated by the behavioral relevance of stimulus features, potentially reflecting recurrent interactions with parietal regions such as area 7a that link sensory information to choices. We tested whether experience-dependent reshaping of V4 representations supports stable readout of task-relevant information and whether this reshaping is coordinated with activity in area 7a. Across two datasets, we quantified the alignment between sensory and choice representations by measuring the similarity between population activity patterns that best predicted stimulus features and those that best predicted the animal's choices. In the first dataset, monkeys made a two-alternative decision based on either color or shape. Although color and shape were represented orthogonally, the V4 choice axis aligned selectively with the currently relevant feature axis. This alignment emerged after feature information appeared and lagged choice-related activity in 7a by approximately 50 ms. This temporal sequence suggests that rotations and scaling of V4 feature representations link task signals to behavioral choices. In the second dataset, monkeys reported the axial curvature of 3D shapes on a continuous scale and made errors when first encountering novel shapes characteristic of few-shot generalization. On these early error trials, V4 responses to novel shapes were displaced from their stable learned representations, and the magnitude of this displacement tracked concurrent activity in area 7a. This relationship was absent for errors on familiar shapes, which suggests that V4 response modulations that are correlated with 7a activity support generalization to novel stimuli. Together, these findings suggest that coordinated activity between parietal and visual cortex accompanies

changes in sensory representations that align task-relevant information with downstream decision processes, enabling flexible behavior across changing task demands and learning.

Disclosures: R. Srinath: None. **M.R. Cohen:** None.

Nanosymposium

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R01EY019041

Title: Primate oculomotor areas and hippocampus support rapid value-based learning and decisions during saccade-based foraging

Authors: *V. SHIRHATTI[1], S. DAVID[2], S. CHANG[4], S. M. LANDI[5], E. A. BUFFALO[6], D. J. FREEDMAN[3];
[1]Dept. of Neurobio., [2]Neurobio., [3]Neurobio. and Computat. Neurosci., Univ. of Chicago, Chicago, IL; [4]Ctr. for Neural Sci., New York Univ., New York, NY; [5]UW Physiol. and Biophysics, [6]Physiol. and Biophysics, Univ. of Washington, Seattle, WA

Abstract: Humans and other animals exhibit a remarkable ability to rapidly learn and generalize behavior across experiences. To study the neural basis of rapid learning in non-human primates we developed a naturalistic foraging-based associative learning paradigm under which monkeys rapidly learned novel stimulus-reward associations in single sessions. In the saccade foraging task (SFT) they freely explored arrays of visual stimuli to harvest chosen targets for rewards, and successfully learned hierarchies based on stimulus features (e.g. color, spatial location, image category; more than 60 problem sets overall across versions) to maximize their rewards. Monkeys were able to solve 2-3 such problems on each day allowing us to compare their behavior and neural responses across multiple oculomotor (frontal eye field (FEF), lateral intraparietal area (LIP), and superior colliculus (SC)) and reward-based learning and memory related (orbitofrontal cortex (OFC) and hippocampus) brain regions (more than 10,000 neuronal units across regions and monkeys) across learning. To understand the various strategies used by the monkeys to solve and learn new problems, we developed a dynamic semi-Bayesian approach that was sensitive to the ongoing context during each harvest and sequences of choices, enabling evaluation of behavioral strategies at the level of individual harvests. These behavioral analyses revealed emergence and evolution of different problem-specific and monkey-specific feature-based and saccade-based strategies across learning. Behavioral strategies and choices reflected

progressively categorical behavior and consolidation of learning for familiar problems across sessions. Abstract encoding of the reward value and the preferred feature which generalized across successively learned problems was observed to varying degrees in all the recorded regions, with the strongest abstractions emerging in FEF and SC. Encoding in hippocampus was more context specific, exhibiting rapid discrimination between stimuli within a problem set during learning, and less generalization across sequentially learned problems. Population responses across the oculomotor network exhibited pre-saccadic planning during foraging, whereas FEF, SC and hippocampus often showed post-saccadic tracking of the ongoing choices. Importantly, shared representations in these areas across successive problems depended on the state of learning, choice preferences and the behavioral strategies. These results suggest complementary roles for these areas during various stages of saccade foraging including planning, monitoring and learning of problem sets.

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T32NS126122, Training Program in Big Data Systems Neuroscience
R01EB026953

Title: Bilateral contributions of FEF neurons during saccade planning

Authors: *E. LOPEZ[1], K. NONEMAN[1], M. A. SMITH[2], J. MAYO[3];
[1]Neurosci. Inst., [2]Biomed. Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA;
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Abstract: Information from one visual hemifield and movement commands directing gaze toward that hemifield are primarily processed by the contralateral hemisphere of the brain. Integrating these lateralized representations into a unified percept and motor response requires precise interhemispheric communication. To investigate how neuronal activity is coordinated across hemispheres in support of coherent oculomotor behavior, we performed dual-hemisphere recordings in the frontal eye fields (FEF), a key prefrontal region involved in visual attention and saccade generation. Using Neuropixels, we simultaneously measured activity from hundreds of

neurons in both FEFs while rhesus macaques performed a memory-guided saccade task. To characterize the structure of population activity within and across hemispheres, we applied dimensionality reduction, allowing us to isolate signals distinct between the hemispheres. We assessed the relationship between latent population dynamics and behavior by using latent factors to predict saccadic reaction times. We were able to measure the relative contributions of hemisphere-specific versus interhemispheric population signals governing oculomotor behavior. We found that global latents predict behavior better than within-hemisphere latents, suggesting that the frontal eye fields act cooperatively, rather than competitively, to resolve conflicting motor plans and produce a singular eye movement. Together, this work provides new insight into the population-level mechanisms by which bilateral cortical networks integrate distributed motor plans into coordinated action.

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Support: HHMI

Title: Dynamic Frontoparietal Communication during Perceptual Decision-Making

Authors: *N. SO[1], A. ZYLBERBERG[1], B. MADEIRA[1], M. N. SHADLEN[2];
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Abstract: Decision-related signals are represented across multiple brain areas, raising a central question in systems neuroscience: how are distributed neural representations coordinated during decision formation? When perceptual decisions are reported by eye movements, several visuomotor areas exhibit remarkably similar decision-related dynamics. Among these, the frontal eye field (FEF) and lateral intraparietal area (LIP) present an informative case, as both areas represent evolving decisions and are densely interconnected. Despite these similarities and reciprocal connections, it remains unclear how neural activity in these areas is coordinated during decision formation.
We simultaneously recorded neuronal populations from FEF and LIP using dual Neuropixels probes while monkeys performed a random-dot motion discrimination task. For each area and recording session, we identified population coding axes for choice using linear decoders and projected single-trial population responses onto these axes to estimate evolving decision signals. Population dynamics in both FEF and LIP exhibited signatures consistent with evidence accumulation: signals evolved reflecting decision difficulty and exhibited drift-diffusion-like variance and autocorrelation structure. Importantly, single-trial fluctuations in FEF and LIP were coordinated in a task-dependent manner. Positive correlations between areas emerged

approximately 200 ms after motion onset, coincident with the appearance of decision-related signals. Analyses of temporal interactions revealed that earlier FEF activity predicted subsequent LIP activity early in the decision process, whereas reciprocal interactions emerged later as the decision evolved toward commitment.
To test the causal contributions of these areas, we performed muscimol inactivation during decisions. FEF inactivation produced robust ipsilateral biases and slowed contralateral choices, whereas preliminary LIP inactivation primarily altered decision timing with comparatively modest effects on choice bias.
Together, these findings suggest that FEF and LIP contribute to decision formation through dynamically coordinated interactions.

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Nanosymposium

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Topic: I.04. Executive Functions

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Title: Emergence of robust persistent activity in frontal cortical circuits

Authors: *C. WANG[1], T. ABE[3], S. DRUCKMANN[4], N. LI[2];
[1]Neurobio., [2]Neurosci., Duke Univ., Durham, NC; [3]Stanford Univ., Palo Alto, CA; [4]Stanford Univ., Stanford, CA

Abstract: Persistent neural activity underlies key cognitive functions such as short-term memory. To produce stable and robust representations, neural circuits must balance between recurrent amplification to prolong network time constants with modular organizations to gate out local perturbations. How such robust persistent representations emerge through learning remains unclear.
Neurons in mouse anterior lateral motor cortex (ALM) exhibit robust persistent activity during motor planning that is maintained by both hemispheres (Li, Daie, et al. Nature 2016; Chen, Kang, et al. Cell 2021). To investigate how these representations form, we longitudinally tracked ALM populations using two-photon calcium imaging as mice learned a short-term memory task. The proportion of task selective neurons and persistent choice activity during short-term memory increased over learning. To probe network robustness, we concurrently used optogenetics to perturb the other ALM hemisphere. Persistent activity was initially fragile to transient perturbations but progressively became robust. These results outline a learning process where frontal cortical circuits first establish persistent representations and subsequently develop modular organization across hemispheres through multi-regional integration.
To better understand how learning gives rise to modular organization in large networks, we

trained recurrent neural networks (RNNs) to generate persistent activity from sensory input and report choice after a delay, mimicking the mouse short-term memory task. We used RNNs with a two-hemisphere architecture, i.e., consisting of two modules with stronger within-module and weaker across-module weights, and a shared readout. Gradient-based training alone in this setup did not produce robustness: silencing one module disrupted activity in the other after training. However, robustness emerged when inputs to each hemisphere were corrupted by independent noise sources, resulting in some trials where one hemisphere received strong sensory inputs while the other received only noise. Under these conditions, the network simultaneously learned persistent activity and developed modular representations capable of mutual error correction, thereby increasing network robustness.
Together, these results reveal the emergence of modular organization in frontal cortical circuits over learning and suggest an unexpected role for the structure of sensory input in shaping robust network organization.

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Topic: I.04. Executive Functions

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5U19NS132720

Title: Brain-wide decision variable modulation reveals single-trial strategy in rats

Authors: *J. A. CHARLTON[1], T. Z. LUO[2], S. C. VENDITTO[5], S. N. OLINE[6], A. G. BONDY[1], W. STAGNARO[1], C. D. KOPEC[3], N. D. DAW[4], C. D. BRODY[7];
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Abstract: Recent behavioral modeling work has shown that rodents can shift their decision-making strategies multiple times within single experimental sessions. In two-alternative forced choice (2AFC) tasks, behavioral estimates of strategy are inherently uncertain. Here we sought to leverage the statistical power granted by large-scale simultaneous electrophysiology to identify rats' strategies at the resolution of single trials and ask how decision strategies modulate neural activity across the brain. Rats were first trained in an auditory accumulation of evidence decision making task, then transitioned to a task with identical stimulus timing and motor demands but a drifting two-armed bandit reward schedule ("Bandit Clicks"). We recorded spikes

simultaneously from up to 1,597 units bilaterally across up to 11 brain regions implicated in decision-making: anterior dorsal striatum (ADS), tail of striatum (TS), primary and secondary motor cortex (M1, M2), prelimbic cortex (PrL), cingulate cortex (Cg1), nucleus accumbens core (NAc), globus pallidus (GP), dorsal subiculum (DS), medial geniculate body (MGB) and dentate gyrus (DG). From each region we independently decoded a time-resolved, one-dimensional decision variable (DV) using logistic regression on activity from each recorded population. We presented repeat trials with identical stimulus sequences, which enabled us to subtract the choice- and stimulus-conditioned mean DV from each trial's DV trace. This allowed us to isolate the 'DV residuals' in each region, i.e. the moment-to-moment fluctuations in the decision process not directly driven by the sensory stimulus or the upcoming choice. K-means clustering of the simultaneously recorded DV residuals (one dimension per region) identified two distinct states that tended to persist across time within a trial, and across trials within a session. In three of four rats, these two states corresponded to leftward and rightward choice biases. Although state identity correlated with action value, it modulated mean choice DV beyond the effect of action value alone in ADS, PrL, Cg1, M1, MGB, TS, and NAc. To measure the decision-related interactions among brain regions, we quantified the cross-region correlation in DV residuals for each simultaneously recorded region pair. When rats made choices that were incongruent with their current bias state, we observed greater cross-region correlation in DV residuals, suggesting stronger coordination. Together these findings suggest that rats' decision strategy can be identified in distributed choice-signal fluctuations and that departures from the current strategy have elevated inter-regional coordination.

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Nanosymposium

NANO10: Executive Control of Perception, Action, and Decision-Making

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Time: Sunday, November 15, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO10.10

Topic: I.04. Executive Functions

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R01-MH139352
R01MH122391
MH13916
U19NS107616

Title: Low-dimensional communication subspaces coordinate hippocampal-cortical dynamics during memory consolidation

Authors: *M. VOROSLAKOS[1], J. GONZALEZ[2], C. LAFFERTY[3], Z. ZHENG[5], D. AYKAN[7], N. SOTO[8], N. NITZAN[6], R. A. SWANSON[5], M. KARADAS[4], Z. S. CHEN[9], G. BUZSAKI[10]; [1]NYU, New York, NY; [2]Dept. of Psychiatry, New York Univ. Grossman Sch. of Medicine, New York, NY, USA, New York, NY; [3]Neurosci. Inst., NYU Langone Hlth., New York City, NY; [4]Neurosci. Inst., NYU Langone Hlth., New York, NY; [6]Neurosci. Inst., [5]New York Univ., New York, NY; [7]Sainsbury Wellcome Centre, Univ. Col. London, London, United Kingdom; [8]ICM-Paris Brain Institute, Sorbonne Université, CNRS, INSERM, Groupe Hospitalier Pitié Salpêtrière, Paris, France; [9]New York Univ. Grossman Sch. of Med., New York, NY; [10]Neurosci., New York University, Langone Med. Ctr., New York, NY

Abstract: How does the hippocampus selectively engage neocortical targets to consolidate memory? Consolidation is thought to depend on coordinated hippocampal-cortical communication during sleep, but the structural and temporal organization of that dialogue remains unclear. Using large-scale electrophysiology (up to 1024 channels) across dentate gyrus, CA3, CA2, CA1, and retrosplenial cortex (RSC) and wide-field cortical imaging in behaving mice, we asked how hippocampal output is partitioned into channels of inter-areal communication and how those channels are activated in time.Using partial canonical correlation analysis, we identified low-dimensional communication subspaces linking upstream hippocampal regions (DG, CA3, CA2) to RSC through CA1. Subspace membership was constrained by intrinsic firing properties and anatomical position, enriched in deep sublayers of the CA3-CA1-RSC axis, and recombined overlapping neuronal pools to support distinct interactions across tasks and brain states. During post-experience sleep, CA1-CA3 subspaces reactivated in register with replay, while CA1-RSC subspaces remained comparatively stable; revealing a plasticity-stability balance along the hippocampal-cortical axis.We next asked how these channels are temporally gated. Hippocampal output during non-REM sleep was organized into clusters of sharp wave-ripples (cSPW-Rs) during cortical UP states, often phase-locked to spindle troughs. Compared with isolated solo ripples, cSPW-Rs preferentially replayed spatially extended trajectories following learning and selectively enhanced segregation between default mode and somatomotor networks.Together, these results suggest a two-tier architecture for consolidation: communication subspaces define the structural channels of hippocampal-cortical dialogue with differential plasticity across the CA3-CA1-RSC axis, while ripple clusters provide the temporal syntax that gates extended replay into appropriate cortical networks. Flexible reconfiguration of predetermined circuit motifs at both structural and temporal levels may underlie how experience is bound into long-term memory.

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Nanosymposium

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HHMI
Raynor Cerebellum Project

Title: Predictive control of mental representations by the primate cerebello-thalamocortical pathway

Authors: *G. M. STINE, M. FAKHARIAN, B. ZHENG, M. JAZAYERI;
MIT, Cambridge, MA

Abstract: The recurrent and interconnected architecture of the neocortex produces complex dynamics that allow mental states to persist, evolve, and guide behavior beyond the immediate demands of the sensory environment. However, this architecture poses a fundamental problem—the brain must control these complex dynamics to flexibly adapt behavior in ever-changing environments. In motor control, a similar problem is solved in part by the cerebellum, which builds internal models that predict the sensory consequences of actions, facilitating real-time corrections to movements and adaptability to environmental perturbations. We asked whether the cerebellum, through its extensive connections with the neocortex via the thalamus, plays an analogous role in cognition by controlling neocortical dynamics that underlie latent mental representations.

To address this question, we developed a novel interval-timing task that translates principles of predictive motor control to the cognitive domain. We trained two macaque monkeys to produce a learned interval to obtain juice reward. On a random half of trials, a visual "flash" occurred at a predictable time, which served as a temporal landmark that monkeys could use to correct their internal clock within and across trials. Based on previous work, we hypothesized that the cerebellum supports these corrections by adjusting the speed of timing-related dynamics in neocortex. Using Neuropixels-NHP probes, we recorded simultaneously from the cerebellar dentate nucleus (DN), the DN-recipient region of ventrolateral thalamus (VL), and the lateral intraparietal cortex (LIP). These recordings revealed distinct but coordinated dynamics across the loop: LIP exhibited canonical ramping dynamics that tracked elapsed time, VL displayed tonic activity that tracked changes in the temporal environment, and DN encoded temporal prediction errors associated with the timing of the flash. Critically, we show that DN responses exhibit hallmarks of a control signal: (1) they preceded and predicted changes in the speed of ramping dynamics in LIP, (2) these changes corrected for errors in the initial speed of ramping, and (3) microstimulation of DN mimicked the corrective effect of the flash itself.

Finally, we show how such a control signal can be computed by a cerebellar circuit model that performs unsupervised learning of the temporal environment, generating testable predictions about the signals present in the cerebellar cortex. Together, the results provide direct evidence that the cerebellum uses similar computations to control both movement and neocortical dynamics.

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Nanosymposium

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NIH R01 NS129098
NIH T32 EB029365
NIH T32 NS126122
NSF GRFP
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Title: Decomposing behavioral variability into sensory and motor components

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Abstract: Consider the start of a race. Sometimes, you respond quickly to the starter pistol, getting out ahead or even false starting. Sometimes, you respond so slowly as to lose the race. What leads to these fluctuations in behavior? A false start could have either a sensory or a motor origin: for example, it could be due to a failure of sensory processing or due to a lowered threshold for action. Observations of behavior alone do not allow us to pinpoint the sources of impulsivity that drives such variability in behavior.
To dissociate between sensory and motor components of behavioral variability, we simultaneously recorded from visual cortex (V4) and motor cortex (M1) while monkeys performed a visual change detection task under time pressure. Animals exhibited considerable variability in their behavior, including many instances where they successfully detected the change, false started, or missed the change entirely.
Taking advantage of our simultaneous multi-area recordings, we made three key discoveries: First, we found that responses in visual cortex to the same stimulus were amplified on false starts and weaker on misses. Second, we found that movement preparation signals in motor cortex were stronger on false starts and weaker on misses. These results suggest that impulsivity-driven variability in behavior is associated with both altered sensory processing and altered motor preparation. Finally, we tested whether sensory processing and motor processing jointly fluctuate from trial to trial, reflecting a common latent signal. We observed that visual and motor cortex made independent contributions to impulsive behavior. In summary, we found that variability in detection behavior can be decomposed into distinct sensory and motor components.

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Title: Dynamic and selective interactions in the motor system during naturalistic reach-to-grasp behavior

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Abstract: When grabbing an object, we reach while preparing and executing a grasp. It remains unclear how distinct streams of action-relevant information (where to reach and how to shape the hand) are shared across brain areas and how these interareal interactions reorganize across different phases of movement. To investigate, we trained a rhesus macaque to perform a naturalistic reach-grasp-lift task, manipulating reach direction and object size while simultaneously recording from dorsal premotor (PMd), ventral premotor (PMv), and primary motor cortex (M1) with Utah arrays. We applied multi-population delayed latents across groups (mDLAG) to identify signals shared between areas and their optimal interareal lags. We asked how interareal interactions changed as a function of (1) movement epoch, and (2) type of information. To study epoch-dependent interactions, we split trials into movement initiation and lift epochs and fit separate mDLAG models for each. We then analyzed the lag-lead structure of all shared signals. During movement initiation, we found that PMd led most shared signals, whereas during lift, M1 led most. This change in the leading brain area supports that information sharing is dynamic throughout movement. Next, to assess how different types of information were shared, we compared the lag-lead structures of latent variables that carried task-informative signals. We quantified three types of information: reach direction, object size, and condition-invariant. Direction and size were each explained by 1 latent with 10s to 100s of milliseconds of lags between areas. However, direction's latent ordered PMd→M1→PMv, while size's proceeded PMd→PMv→M1. Further, condition-invariant signals were captured by 4 latents which only exhibited 1s to 10s of milliseconds of lag between areas. These results illustrate different types of movement information being coupled and shared between different areas at different times. Our combined findings support the notion that dynamic and selective interactions between motor cortical areas underlie naturalistic reach-to-grasp behavior: while PMd, PMv, and M1 all encode reach and grasp information, the timing and content of interareal signals reflect structured differences aligned with potentially specialized roles.

Disclosures: A.L. Smoulder: None. **N. Carr:** None. **C. Chandrasekaran:** None.

Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

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Presentation Number: NANO11.01

Topic: B.08. Epilepsy

Support: NINDS (NS102609)
WWOX Foundation

Title: Cellular and circuit dysfunction driving targeted therapy in WWOX epilepsy

Authors: *M. NAPPI[1,2], S.-N. LAU[1,2], C. ALDAZ[3], X. JIANG[1,2];
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Abstract: Biallelic loss-of-function variants in *WWOX* cause severe developmental and epileptic encephalopathies characterized by early-onset seizures and limited therapeutic options. However, the cellular and circuit mechanisms underlying seizure susceptibility remain poorly understood. Here, we investigated the consequences of *Wwox* deficiency using complementary genetic mouse models, electrophysiological recordings, imaging, and electroencephalographic monitoring. Our findings indicate that interneuron dysfunction contributes to the epileptic phenotype associated with *Wwox* loss. These changes may compromise inhibitory control within cortical networks and promote seizure generation. We further evaluated a pharmacological strategy aimed at improving interneuron function. Treatment partially restored firing properties *in vitro* and reduced seizure burden *in vivo*. Together, these results identify a cell-type-specific circuit mechanism contributing to WWOX-related epilepsy and support the development of targeted therapeutic approaches for genetic epileptic encephalopathies.

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Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

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Topic: B.08. Epilepsy

Support: CAS institutional support RVO:61388963
GA UK: 494226

Title: Novel synthetic neurosteroid PPG offers distinctive mechanisms of anti-seizure protection in the pentylenetetrazol animal model of limbic epilepsy.

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Abstract: Despite decades of epilepsy research, approximately one-third of patients have pharmacoresistant epilepsy, highlighting the need for therapies with mechanisms distinct from commonly used medications. Neurosteroids are promising antiseizure candidates because they positively modulate both synaptic and extrasynaptic $GABA_A$ receptors. However, their effects on neuronal circuit dynamics in vivo remain poorly understood. We used simultaneous two-photon calcium imaging and single-channel electrocorticography (ECoG) to compare a newly developed synthetic neurosteroid pregnanolone pyroglutamate (PPG) with lorazepam under physiological conditions and during pentylenetetrazole (PTZ)-induced seizures. PV-tdTomato C57BL/6J mice (n=9) were implanted with a cranial window and injected with an AAV encoding jGCaMP8m, enabling separation of calcium activity in parvalbumin-positive interneurons (PV-INs) and non-PV, predominantly pyramidal, neurons. CaSCaDe was used to infer spiking activity from raw calcium traces. Animals were imaged for 2 h after oral administration of PPG (150 mg/kg), lorazepam (5 mg/kg), or vehicle. In subsequent drug-vehicle-drug trials, PTZ (35-50 mg/kg) was administered after each treatment to test whether each compound suppressed seizure-related activity. Under baseline conditions, compared with vehicle, both lorazepam and PPG mildly reduced PV-IN CaSCaDe-inferred activity, whereas only PPG reduced inferred spiking activity in non-PV neurons by 44±14% (mean±SD). ECoG analysis of total signal power indicated that lorazepam-associated effects lasted <45 min, whereas PPG-associated changes persisted throughout the 2 h recording. PPG did not produce overt sedation despite the high dose used. Power spectral density analysis revealed a prominent 5-6 Hz ECoG peak in PPG-treated animals that persisted during PTZ administration, consistent with previously reported neurosteroid-associated modulation of extrasynaptic $GABA_A$ receptor activity. By contrast, lorazepam produced a mild increase in β-band power that was abolished after PTZ induction. While both drugs prevented PTZ-induced seizures, these findings show that neurosteroid modulation produces circuit and ECoG-level effects distinct from benzodiazepine treatment. Finally, a subsequent experiment showed that PPG prevented seizures even when PTZ was given at a supralethal dose of 150 mg/kg, whereas lorazepam only prevented death. PPG reduced cortical excitatory neuronal activity and maintained network effects during PTZ challenge, supporting further evaluation of synthetic neurosteroids as candidate therapies for pharmacoresistant epilepsy.

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Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO11.03

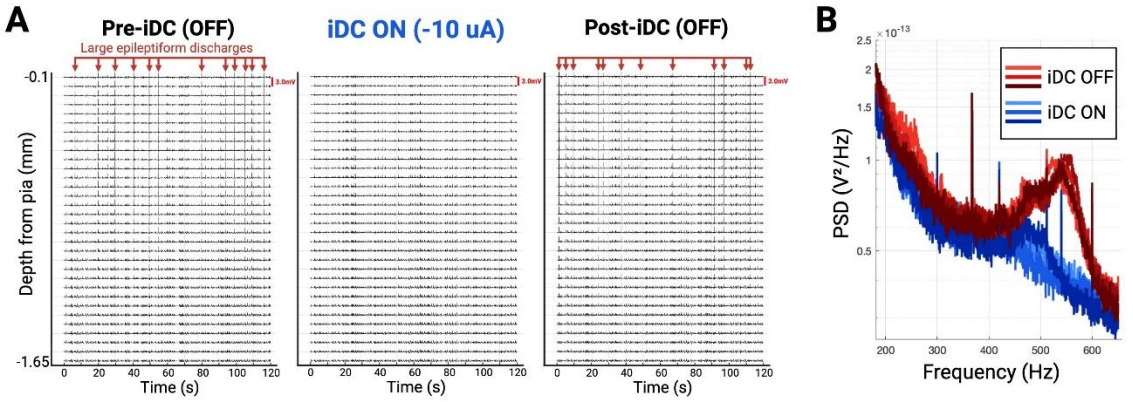
Topic: B.08. Epilepsy

Support: 1R01NS146406-01
R01NS110893

Title: Focal ionic direct current suppresses epileptiform discharges in rat cortex and computational models

Authors: *R. WANG[1], F. S. BORGES[3,4,5], S. DURA-BERNAL[5,6], G. FRIDMAN[2,1]; [1]Biomed. Engin., [2]Otolaryngology, Johns Hopkins Univ., Baltimore, MD; [3]Physiol. and Pharmacol., State Univ. of Ponta Grossa, Ponta Grossa, Brazil; [4]Ctr. for Computation, Mathematics and Cognition, Federal Univ. of ABC, São Paulo, Brazil; [5]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [6]Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Focal epilepsy arises from local circuit hyperexcitability, yet current neuromodulation therapies often act after seizure detection or through broad network targets. We tested ionic direct current stimulation (iDC) as a focal, mechanism-driven therapy designed to suppress the epileptogenic generator by locally shifting cortical excitability, combining acute rat experiments with a biophysically detailed thalamocortical model. Sustained DC can modulate excitability, but conventional metal electrodes risk electrochemical reactions and toxic byproducts during prolonged current delivery. iDC delivers DC on the pia surface through an electrolyte-filled microcatheter, separating metal-electrode reactions from cortex while enabling focal, low-amplitude modulation. In an acute urethane-anesthetized rat preparation, penicillin G was focally injected into somatosensory cortex (500 IU, 2.5 µL) while laminar LFP/MUA was recorded with a 32-channel silicon probe. Penicillin induced recurrent large-amplitude multichannel epileptiform discharges with elevated high-frequency power. Cathodic iDC delivered near the penicillin focus (<200 µm; −10 µA) suppressed these discharges during repeated ON blocks, with re-emergence during neighboring OFF blocks. Detected large-discharge rate decreased from 5.25-8.63 events/min during OFF to 0-1.25 events/min during ON. Power spectral density analysis of unfiltered wideband recordings showed corresponding reduction of high-frequency power, especially in the fast-ripple range (~250-600 Hz). In parallel, the model generated HFO-like laminar LFP activity and reproduced iDC-dependent LFP and PSD suppression, supporting a mechanism in which cathodic DC reduces pathological synchrony by shifting local excitability. These preliminary results suggest that focal cathodic iDC can suppress epileptiform discharges and fast-ripple-band activity by locally controlling the epileptogenic focus.



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Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

Location: WCC Rm 140

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Topic: B.08. Epilepsy

Support: CureSyngap1
MCHRI
Wu Tsi Neuroscience

Title: Preclinical Evidence for Nortriptyline as a Precision Therapeutic for SYNGAP1-Related Neurodevelopmental Disorder

Authors: *A. EBRAHIM AMINI[1], P. M. KLEIN[7], T. YANG[8], L. WU[9], N. PERFITO[10], A. GUIN[10], U. LEONE HADITSCH[11], N. OMAR[2], L. PENG[12], L. ANDRADE[3], F. MILLION[4], C. W. LEE-MESSER[5], R. LEVY[6], F. M. LONGO[13], I. SOLTESZ[1], C. MOXHAM[10], J. K. KNOWLES[14];
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Abstract: The gene SYNGAP1 encodes a Ras/Rap GTPase-activating protein that plays an essential role in synaptic development and plasticity in early brain development. Pathogenic variants in one copy of SYNGAP1 that cause haploinsufficiency are linked to a pediatric

neurodevelopmental disorder (SYNGAP1-NDD) that includes epilepsy, autism, and intellectual disability. At present, there are no approved therapies that specifically target SYNGAP1 haploinsufficiency or the resulting NDD. Approximately 500 small molecules, including FDA-approved drugs, were initially screened using RNA sequencing in human induced pluripotent stem cell-derived glutamatergic neurons. Among the screened drugs, a tricyclic antidepressant, nortriptyline, most effectively reversed disease-associated gene expression profiles in patient-derived neurons, particularly within pathways related to synaptic signaling and glutamatergic function. In the Syngap1+/c.3583-9G >A (Syngap1+/-) mouse model, seizure severity progressively increased between postnatal day 60 (P60) and P120, which was accompanied by cognitive and behavioral impairments. Intraperitoneal administration of Nortriptyline (3 mg/kg) or vehicle was initiated at P120 and continued for 30 days, i.e. beginning at a stage when both epilepsy and behavioral impairments were already established. At P150, critically, Syngap1 protein levels, which were reduced to 64% of wild-type levels in vehicle-treated Syngap1+/- mice, were restored to wild-type levels following nortriptyline treatment. Additionally, the significant increase of phosphorylated ERK in the vehicle-treated Syngap1+/- mice, was normalized by nortriptyline treatment. Whereas vehicle-treated Syngap1+/- mice exhibited clear LTP deficits, these were reversed in nortriptyline-treated Syngap1+/- mice. Nortriptyline treatment of Syngap1+/- mice prevented epilepsy progression, reduced hyperactivity, and restored spatial working memory and social behavior, to performance comparable to vehicle-treated wild-type mice.Taken together, these preclinical results suggest that nortriptyline, an FDA approved drug which is used in children, holds promise as a precision therapeutic for SYNGAP1-NDD, by directly restoring SYNGAP1 expression levels and improving synaptic function. Further, restoration of SYNGAP1 expression by nortriptyline can provide therapeutic benefit even after the onset of epilepsy and cognitive/behavioral impairments, indicating that disease phenotypes in SYNGAP1-NDD may be at least partially reversible.

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Nanosymposium

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Topic: B.08. Epilepsy

Support: P50MH136297

Title: Distinct hepatic and astrocytic mechanisms segregate seizure and non-seizure phenotypes in ALDH7A1 deficiency

Authors: *A. SAITO[1], T. E. FAUST[5,2], S. ISHIKAWA[2], K. ISHIZUKA[3], A. SAWA[2,1,3,4,6]; [1]Physiology, Pharmacology, and Therapeut., [2]Neurosci., [3]Psychiatry, [4]Biomed. Engineering,

Genet. medicine, Johns Hopkins Univ., Baltimore, MD; [5]Univ. of Massachusetts Chan Med. Sch., Worcester, MA; [6]Mental Hlth., Johns Hopkins Sch. 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. Here, we demonstrate that the clinical pleiotropy of co-occurring seizure and non-seizure psychiatric phenotypes caused by the same epilepsy gene is explained by distinct hepatic and prelimbic astrocytic mechanisms, respectively, thereby providing a model for mechanism-specific precision medicine.

Patients with epilepsy often experience seizures and persistent psychiatric symptoms, yet it remains unclear whether these clinical domains arise from the same disease mechanism or distinct biological processes. Pyridoxine-dependent epilepsy (PDE), a hereditary form of epilepsy caused by ALDH7A1 mutations, features both seizure-associated phenotypes treated with vitamin B6, and psychiatric and cognitive symptoms non-responsive to treatment. We used an Aldh7a1 knockout model to address this enigma. Global Aldh7a1 knockout mice showed increased pentylenetetrazol-induced seizure susceptibility and maladaptive affective behaviors, which captured the key behavioral features of the disease. Notably, hepatocyte-specific Aldh7a1 knockout mice recapitulated seizure susceptibility but showed no affective behavioral deficits. In contrast, astrocyte-specific knockout mice displayed affective behavioral deficits without increased seizure susceptibility.

We next asked the mechanism of how the loss of astrocytic ALDH7A1 alters brain function. Transcriptomic and biochemical approaches with a redox sensor showed impaired astrocytic redox homeostasis, reducing NRF2 signaling and eliciting a GSH/GSSG imbalance. We also observed that these astrocytic abnormalities resulted in the reduction of pyramidal neuronal excitability in the prelimbic layer 5, relevant to accounting for maladaptive affective behaviors. Dietary sulforaphane restored the prelimbic neuronal activity and rescued the behavioral deficits. Astrocyte-specific molecular reinstatement of ALDH7A1 or NRF2 also rescued neuronal activity.

To further characterize the liver-mediated seizure mechanism, we are currently performing metabolomic profiling of liver, plasma, and brain samples from hepatocyte-specific Aldh7a1 knockout mice.

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American Epilepsy Society Postdoctoral Fellowship

Title: Corneal Kindled Alzheimer's Disease-Related Mice Address Mechanisms of and Preventative Treatments for Sudden Unexpected Death in Epilepsy

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Abstract: Background: Sudden unexpected death in epilepsy (SUDEP) is a multifactorial outcome of devastating clinical consequence. Unfortunately, current preclinical models do not address all biological aspects of SUDEP. We have reported that young corneal kindled APP/PSEN1 mice, an Alzheimer's disease (AD) model, experience significant premature mortality and serotonin (5-HT) system dysfunction prior to AD pathology onset (Del Pozo et al, *Prog Neurobiol* 2024), mimicking important aspects of SUDEP. We thus hypothesized that corneal kindled APP/PS1 mice represent a novel SUDEP model and aimed to prospectively document spontaneous seizure-induced death using video-EEG (vEEG) for potential pharmacological SUDEP prevention. **Methods**: APP/PS1 and transgene-negative (Tg-) mice were implanted for vEEG at 4-5 weeks-old (7 males, 5 females). After recovery, mice were corneal kindled (3 sec, 60 Hz 1.6-2.0 mA; n=6) twice daily until kindled (five consecutive Racine stage 5 seizures). Sham-kindled controls (n=6) received handling without corneal stimulation. vEEG was recorded during the dark cycle in a consecutive 10-day period during kindling to document SUDEP events. A second cohort were treated prior to each kindling stimulation with 5-HT modulators - lorcaserin (10 mg/kg), cannabidiol (100 mg/kg), or fenfluramine (FFA; 15 mg/kg) to attempt to prevent SUDEP. **Results**: In the vEEG cohort, 3/6 APP/PS1 mice died during kindling versus 0/7 Tg- mice ($p<0.03$), including two APP/PS1 mice with vEEG confirmed spontaneous seizures immediately preceding death and one in-hand after a kindled seizure. While repeated FFA administration normalized kindling rate of APP/PS1 mice in the intervention cohort, it did not significantly reduce seizure-induced premature mortality (5/9 FFA-treated APP/PS1 mice died during kindling versus 0/7 Tg- mice, $p<0.02$). CBD and LORC did not confer benefit. **Conclusions**: Corneal kindled APP/PS1 mice offer a novel, inducible adult-onset SUDEP model. The observed SUDEP events and documented spontaneous seizures offer a novel paradigm for longitudinal studies of SUDEP-related mechanisms and interventions.

Disclosures: M. Barker-Haliski: A. Employment/Salary (full or part-time):; University of Washington. **S. Davidson:** A. Employment/Salary (full or part-time):; University of Washington. **A. Del pozo sanz:** A. Employment/Salary (full or part-time):; University of Washington. **Q. Wu:** A. Employment/Salary (full or part-time):; University of Washington.

Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO11.07

Topic: B.08. Epilepsy

Support: NIH NINDS/NIGMS R01NS1344914

Title: Mechanisms for Heterogenous Outcomes in Tuberous Sclerosis Complex

Authors: *E. E. DEAN[1], M. K. LARA[2], A. PEZZUTO[3], M. MAHONEY[4], A. E. HERNAN[5]; [1]Nemours Children's Hosp., Wilmington, DE; [2]Univ. of California San Diego, La Jolla, CA; [3]Univ. of Delaware, Newark, DE; [4]Jackson Lab., Bar Harbor, ME; [5]Neurolog. Sci., Nemours Children's Health/University of Delaware, Wilmington, DE

Abstract: Tuberous Sclerosis Complex (TSC) is an autosomal dominant neurodevelopmental disorder resulting from a loss of function (LoF) mutation on either the *TSC1* or *TSC2* genes and is a leading genetic cause of epilepsy, which effects up to 90% of patients. Additionally, about 90% of patients will be diagnosed with a TSC-associated neuropsychiatric disorder (TAND). Classical models of TSC rely on conditional knockouts (KO) in specific neural populations to recapitulate these hallmark neurological symptoms. These models lack construct validity and are therefore limited in their translational and therapeutic utility. Historically, germline heterozygous models of TSC, which have construct validity, do not model epilepsy or TANDs in adulthood and therefore lack face validity. Here, we suggest a relationship between genetic background and Tsc1 haploinsufficiency. We show that we can harness this relationship to recapitulate TSC-associated epilepsy and neuropsychiatric disorders. We generated a new congenic strain on a pure C67BL/6J (B6) background to create B6-*Tsc1*$^{+/-}$ mice, which we bred to make F1 hybrids with the DBA/2J (D2) strain (D2-Tsc1$^{+/-}$) and the BXD87/RwwJ (BXD87) strain (BXD87-*Tsc1*$^{+/-}$). We phenotype these mice using a full behavioral panel, 24/7 home cage seizure monitoring, and molecular and histological analysis to identify the complex role of genetic background on *Tsc1* haploinsufficiency. We found that genetic background changes seizure penetrance, with all strains showing low penetrance for seizures. 15% (4/27) of B6-*Tsc1*$^{+/-}$, 12% (5/43) of BXD87-*Tsc1*$^{+/-}$, and 5% (1/18) of D2-*Tsc1*$^{+/-}$ mice had spontaneous seizures in adulthood. Genetic background also impacts TAND phenotypes: BXD87-*Tsc1*$^{+/-}$ mice show an anxiety phenotype in the Light/Dark Box task, and BXD87-*Tsc1*$^{+/-}$ and D2- *Tsc1*$^{+/-}$ show a cognitive impairment phenotype in the Barnes Maze. Molecularly, B6-*Tsc1*$^{+/-}$ and D2-*Tsc1*$^{+/-}$ mice show increased in GFAP expression in the hippocampus. These results show, for the first time, that heterozygous mouse models of Tsc1 can recapitulate the primary neurological symptoms of TSC. Furthermore, we show the importance of genetic background on symptomology in this disease.

Disclosures: E.E. Dean: None. **M.K. Lara:** None. **A. Pezzuto:** None. **M. Mahoney:** None. **A.E. Hernan:** None.

Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO11.08

Topic: B.08. Epilepsy

Title: Short-Term Intranasal Delivery of Human Breast Milk-Derived Exosomes as a Potential Therapy in Hypoxia-Induced Neonatal Seizures

Authors: *O. TAPARLI[1], X. GUO[2], K. KLINKHAMMER[2], S. L. CAMPBELL[3], B. SIMS[4]; [1]Dept. of Neonatal/Perinatal Med., [3]Animal and Poultry Sciences/ Sch. of Neurosci., [2]Univ. of Alabama at Birmingham, Birmingham, AL; [4]Div. Neonatol/Dept Pediat, Univ. of Alabama at Bham, Birmingham, AL

Abstract: Hypoxic-ischemic encephalopathy (HIE) is the leading cause of neonatal seizures and associated long-term neurodevelopmental morbidity, including cognitive and motor impairments. Current antiseizure therapies have limited efficacy and carry potential neurodevelopmental toxicity, underscoring the need for novel interventions. Human breast milk-derived exosomes (HBM-Exo) are naturally occurring extracellular vesicles enriched with bioactive cargo, including proteins, lipids, and nucleic acids, and have been reported to cross the blood-brain barrier. Emerging evidence suggests that HBM-Exo can modulate neuroinflammatory responses and influence synaptic signaling pathways, positioning them as promising candidates for neuroprotection in neonatal brain injury. We investigated the effects of intranasally administered HBM-Exo (25 μg; 2.5 μL/nostril) in the Jensen neonatal mouse model, in which global hypoxia induces HIE-associated neonatal seizures. Male and female C57BL/6 pups were assigned to three groups: normoxic controls receiving no treatment (CTR, n=6), hypoxia-exposed pups receiving no treatment (HX, n=6), and hypoxia-exposed pups receiving HBM-Exo pretreatment at postnatal day 6 and postnatal day 7, followed by hypoxia induction. Sex differences were not assessed and data were pooled across sexes. Seizure activity was assessed by blinded Racine scale scoring; total seizure number, convulsive seizure frequency, and latency to seizure onset were quantified. Groups were compared by one-way ANOVA with Tukey's post-hoc correction for all outcomes. HX group showed significantly increased total seizures (63.2 ± 5.19 vs 22.7 ± 3.59 in CTR; $p < 0.0001$) and convulsive seizures (6.8 ± 1.70 vs 1.5 ± 0.96; $p = 0.023$), and reduced latency to onset (127.8 ± 39.0 vs 574.8 ± 51.1 s; $p < 0.0001$), validating the model. Within this short treatment paradigm, HX+HBM-Exo treated pups exhibited trends toward reduced convulsive seizure frequency compared with HX pups (2.7 ± 0.97 vs 6.8 ± 1.70; $p = 0.072$), with values comparable to CTR pups ($p = 0.76$). Total seizure number was also reduced in HX+HBM-Exo treated pups compared to HX pups (47.9 ± 4.93 vs 63.2 ± 5.19; $p = 0.079$). All values are mean ± SEM. Although these findings did not reach statistical significance, preliminary data from this initial study suggest that intranasal HBM-Exo may attenuate seizure burden following hypoxic insult. These results warrant further investigation in larger cohorts and with extended treatment durations to better define efficacy. Ongoing molecular analyses are expected to provide critical insight into the mechanistic basis underlying these effects.

Disclosures: O. Taparli: None. **X. Guo:** None. **K. Klinkhammer:** None. **S.L. Campbell:** None. **B. Sims:** None.

Nanosymposium

NANO11: Mechanism-Based Therapeutics for Developmental and Acquired Epilepsy

Location: WCC Rm 140

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO11.09

Topic: B.08. Epilepsy

Title: Effect of Intracerebroventricular M1 Muscarinic Receptor Blockade on Spike-and-Wave Discharges in Genetic Absence Epilepsy Rats

Authors: Ö. ŞAKA[1], A. TOPLU HOCAOğLU[2], Ö. DEMIR[1], B. YıLDıRıM[1], M. AYDıN[1], M. ÇAVUş[3], I. H. ULUS[4], ***F. ONAT**[1];
[1]Acibadem Univ., Istanbul, Turkey; [2]Hlth. Sci. Univ., Istanbul, Turkey; [3]Istanbul Univ., Istanbul, Turkey; [4]Okan Univ., Istanbul, Turkey

Abstract: Purpose: Childhood absence epilepsy is a sub-group of genetic generalized epilepsies that is characterized by spike-and-wave discharges (SWDs) on electroencephalography (EEG), along with behavioral changes. M1 muscarinic receptors are widely expressed in the cerebral cortex, hippocampus, and striatum, suggesting an important role in cholinergic modulation of neuronal excitability and related circuits. However, their specific contribution to absence seizure activity remains unclear. Therefore, this study aimed to investigate the effects of intracerebroventricular (i.c.v.) pirenzepine, a selective M1 muscarinic receptor antagonist, on SWDs in Genetic Absence Epilepsy Rats from Strasbourg (GAERS). Method: This prospective controlled trial tested i.c.v. saline (n=6), pirenzepine 100 nmol (n=6), and pirenzepine 300 nmol (n=6). Adult male and female GAERS (3-4 months old, 250-350 g) underwent stereotaxic surgery under isoflurane anesthesia for intracerebroventricular (i.c.v.) guide cannula implantation and EEG electrode implantation in the frontal and parietal cortices, based on the rat brain atlas. EEG recordings were performed for 180 minutes at saline and post-injection periods. SWD analysis was conducted using LabChart v7 (PowerLab 8/35, ADI Instruments) and 2-way ANOVAs were applied for statistical comparisons. Results: Following saline baseline recordings, 300 nmol i.c.v. pirenzepine significantly reduced cumulative SWD duration during the first 20 min post-injection in GAERS, whereas 100 nmol pirenzepine showed no significant suppression at any time point. Dosage group comparisons from 3-hour EEG recordings for cumulative SWD durations were as follows: [Saline 0-20 min: (531.1 ± 111.5 sec), Pirenzepine 100 nmol post-injection 0-20 min: (528.2 ± 294.6 sec), and Pirenzepine 300 nmol post-injection 0-20 min: (223.6 ± 320.1 sec)]. Pirenzepine 300 nmol significantly reduced cumulative SWD duration compared with the other groups ($p < 0.05$). However, no significant difference was observed between groups in cumulative or mean of single SWD durations, or the number of SWDs when the total 180-min EEG recording period was analyzed. Conclusion: The intracerebroventricular administration of pirenzepine in GAERS produced a significant but transient suppression of SWDs during the first 20-minute post-injection period. Further research is needed to clarify the specific role of M1 muscarinic receptors in the cholinergic modulation of absence epilepsy.

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Nanosymposium

NANO12: Alzheimer's Disease: Omics

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO12.01

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

Title: Brain cell type-specific metabolic crosstalk drives lipid homeostasis disruption in Alzheimer’s Disease

Authors: *B. JIANG, P. BALONI;
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Abstract: Background: Metabolic changes associated with lipid metabolism, especially accumulation of lipid droplets (LDs) in the brain, are important pathophysiological features of Alzheimer’s Diseases (AD). Studies have shown brain cell type-specific metabolic alterations leading to AD pathophysiology, but the systems-level metabolic rewiring and intercellular interactions between cell types leading to LD accumulation remain understudied. **Method:** Using post-mortem brain single-nucleus RNA-sequencing (snRNA-seq) data from two large AD cohorts, the Religious Orders Study and Memory and Aging Project (ROSMAP) and Seattle Alzheimer’s Disease Brain Cell Atlas (SEA-AD), we developed *BrainMultiCell-GEM*, the first manually curated and integrated genome-scale metabolic network of human brain cell types. This *in silico* model effectively captures neuronal, astrocytic, and microglial metabolism, enabling simulation of both intracellular metabolic states and intercellular metabolic crosstalk. We also developed a Bayesian optimization framework to enhance *in silico* simulation of AD-associated, brain cell type-specific metabolic rewiring. Transcriptional factors (TFs) associated with cell type-specific lipid dyshomeostasis in AD were identified via a machine learning model using transcriptomic and metabolic profiles. **Results:** *BrainMultiCell-GEM* consists of 7511 metabolites, 11067 metabolic reactions, and 6400 genes. Integration of snRNAseq data from ROSMAP and Neuropsychiatric Symptoms in Alzheimer's Disease (NPS-AD) studies, our metabolic flux simulations consistently predicted increased LD accumulation in AD brains, particularly in microglial cells, concordant with brain atrophy and disrupted energy metabolism. We also observed metabolic alterations in glycerophospholipid metabolism and fatty acid oxidation in AD microglia and astrocytes. These alterations were associated with dysregulation of *PNPLA3* and *LIPC* genes in microglia, *ELOVL2* and *CPT1B* genes in astrocytes, highlighting cell type-specific metabolic changes. Our analysis also identified TFs regulating signaling pathways associated with disrupted lipid metabolism in AD brain cells, especially the SUMOylate target proteins pathway involving *NR3C1*, *PPARA*, and *PIAS1*. **Conclusion:** *BrainMultiCell-GEM* enables systematic interrogation of brain cell type-specific metabolism and intercellular crosstalk, identifying mechanisms of lipid dysregulation and metabolic failure that contribute to AD pathogenesis and paves way for future therapeutic interventions.

Disclosures: B. Jiang: None. **P. Baloni:** None.

Nanosymposium

NANO12: Alzheimer's Disease: Omics

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Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO12.02

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

Support: SFNS grant 310030_212322

Title: Spatial multi-omics identifies a plaque-distant white-matter-like inflammatory gradient in human Alzheimer's disease hippocampus

Authors: *A. M. BADINA[1], S. TSARTSALIS[2], L. ABJEAN[3], K. CEYZÉRIAT[4], P. MILLET[3], B. B. TOURNIER[3];
[1]Univ. of Geneva, Geneva, Switzerland; [2]Psychiatry, [3]Univ. of Geneva / Univ. Hosp. of Geneva, Geneva, Switzerland; [4]CIBM Ctr. for Biomed. Imaging, Geneva, Switzerland

Abstract: Alzheimer's disease (AD) neuropathology is defined by amyloid-β (Aβ) plaques and tau tangles accumulation, and neuroinflammation thought to damage neurons. However, these lesions do not fully explain when and where inflammatory pathology emerges in human hippocampus. Here, we characterize AD-associated glial activation and inflammation relative to plaque location. We analyzed human postmortem hippocampus using 10x Visium spatial transcriptomics with Aβ plaque annotation (control n=7, AD n=9; Braak I-VI), bulk DIA proteomics (control n=6, early AD n=12, late AD n=13; Braak II-VI), public single-nucleus reference deconvolution, and an independent immunohistochemistry cohort spanning young, Aβ-negative control, Aβ-positive non-demented, early AD, and late AD cases (n=54). Spatial models were run within histology-defined grey-matter-like (GML) and white-matter-like (WML) hippocampal compartments, preventing plaque distance from acting as a proxy for compartment identity. Aβ plaques were much more present in neuron-rich compartments. Overall, 8.10% of GML spots were plaque-positive versus 1.27% of WML spots, a 6.4-fold difference. In contrast, inflammation was stronger in WML, far from neuron-rich compartments. A pre-specified 49-module inflammatory taxonomy identified a plaque-distant WML field enriched for reactive-glial, extracellular-matrix remodeling, iron-handling, complement system, AGE-RAGE/NF-κB, glymphatic, and ferroptosis-related programs. Thirteen modules showed the WML-far/GML-near pattern, with slide-level directional concordance across compartment and diagnosis cells. In proteomics, six field modules increased with continuous Braak stage after adjustment for age, sex, and postmortem delay, and a composite FrontIndex tracked Braak severity. Cell-type deconvolution attributed the field mainly to astrocytes, microglia, and a glio-vascular axis; nine of ten pre-specified cellular predictions were recovered. In the IHC cohort, Aβ-positive non-demented cases retained low IBA1 signal whereas early AD showed marked microglial activation, supporting plaque insufficiency as an explanation for inflammatory state. These data indicate that AD hippocampus contains a plaque-distant, WML-enriched inflammatory field that is glial, temporally progressive, and oxidative/carbonyl-stress-compatible. Rather than treating neuroinflammation as only a local response to plaques, this framework identifies WML glial and glio-vascular biology as a candidate driver or amplifier of disease progression. Inflammation thus seems to start far from Aβ plaques, and progress inwards neurons with the disease.

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Nanosymposium

NANO12: Alzheimer's Disease: Omics

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

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Office of The Director, and National Institutes of Health (OD, 3P20GM121310-07S2)

Title: Transcriptomic and Epigenomic Profiling Reveal a Core Alzheimer's Disease Signature Distinct from Normal Aging in 5xFAD Mice

Authors: *M. SCHULTZ, Q.-Q. SUN;
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Abstract: Alzheimer's disease (AD), the most prevalent form of dementia, is a major contributor to US mortality, with current therapies providing limited benefit. Its multifactorial nature means reductionist approaches incompletely capture the complex biological networks underlying AD pathophysiology.We utilize scRNAseq and Visium HD spatial transcriptomics to characterize molecular changes during AD progression in 14-week and 12-month 5XFAD homozygote mice relative to wildtype (WT) controls. Leveraging the higher spatial resolution of Visium HD (2µm), we resolve 40 spatial clusters compared to 34 identified by scRNAseq. Pseudobulk analysis using a Generalized Linear Model (GLM) isolates the age-by-genotype interaction, enabling separation of disease-specific aging signatures from natural aging.scRNAseq revealed 111 significant genes (FDR < 0.05 & |logFC| > 1), including 36 unique to AD-specific aging forming a high-confidence core transcriptomic signature. These genes were enriched in metabolism, ER processing, chaperoning, trafficking, and signaling. Notably, 16 genes encode proteins not previously linked to AD but connected to known biomarker networks, suggesting novel therapeutic targets. Cell-cell communication topology remained largely preserved, with 168 shared ligands versus 27 AD-specific and 43 WT-specific, suggesting AD preferentially disrupts intracellular signaling rather than network connectivity. Spatial mapping revealed strong membrane/vesicle and synaptic gene expression in the hippocampus, thalamus, and entorhinal cortex. Visium HD further resolved the temporal progression of these molecular changes with regional precision. At 14 weeks, synaptic and RNA processing gene downregulation constitute an early molecular damage signature alongside moderate amyloid beta plaque accumulation

(36.14%), which continues to increase with disease progression, reaching 46.32% by 12 months alongside ER/trafficking dysregulation, metabolism disruption, and glial activation. We will present newly generated Visium HD spatial transcriptomics data and compare these findings with existing scRNAseq datasets. This analysis highlights the complementary strengths of each platform and reveals both shared and distinct molecular features across AD progression. We will also present ATACseq profiling from the same age groups to capture broader chromatin-level coordinated signaling networks and upstream genomic regulation. Together, these datasets identify molecular programs distinguishing AD-specific changes from natural aging, highlighting the need for multi-target approaches to capture full disease complexity.

Disclosures: M. Schultz: None. **Q. Sun:** None.

Nanosymposium

NANO12: Alzheimer's Disease: Omics

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

Support: NIH RF AG051504
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FL_DoH_22A06

Title: Microglial profiling of Alzheimer’s disease low-frequency risk variant carriers reveals disease signatures

Authors: *Ö. IS[1], J. TAN[1], A. GADDI[2], X. WANG[2], J. BERGMAN[1], F. TUTOR-NEW[1], M. HECKMAN[2], W. TSAI[1], M. ATIK[1], J. S. REDDY[2], T. KANEKIYO[3], D. W. DICKSON[1], M. ALLEN[1], N. ERTEKIN-TANER[1];
[1]Neurosci., [2]Quantitative Hlth. Sci., Mayo Clin., Jacksonville, FL; [3]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL

Abstract: Introduction: Alzheimer's disease (AD) impacts all brain cells as detected by multiomic and functional cellular analyses. Prior studies have identified missense variants in genes involved with immune functions including *PLCG2* and *ABI3*, which can either impair or enhance microglial function. Our goal is to identify the molecular signatures in microglia associated with these AD protective and risk variants, aiming to clarify their impact on transitions between microglial subtypes and progression of AD pathology. **Methods:** We generated microglia-enriched snRNAseq data from 30 donors carrying *ABI3* AD-risk or *PLCG2* AD-protective missense mutations, or neither. We performed differential expression analysis between variant carriers and non-carriers. A “protective signature” was defined as genes upregulated with the *PLCG2* protective and downregulated with the *ABI3* risk allele, while the

inverse defined a “risk signature.” We assessed the directional changes of these signatures in snRNAseq datasets from donors at different stages of AD neuropathology. We constructed pseudotime trajectory (PT) of microglial transcriptome in these datasets. We determined the change of signatures in microglia trajectories. To further relate these signatures to microglial subtypes, we also annotated the trajectories for microglial subtypes from microglial RNAseq studies. We validated our signatures and their impact on microglial subtype transitions using scRNAseq data from iPSC-derived microglial-like (iMGL) cells. **Results:** We generated snRNAseq profile of 35,000 microglia cells from individuals carrying AD-associated *ABI3* or *PLCG2* variants. We identified 227 protective and 293 risk signature genes linked to these variants. Protective signature genes were downregulated in early phases of AD neuropathology but upregulated in late phases, while risk genes exhibited the opposite pattern. PT analysis revealed that cells with protective signatures show a relative alignment with homeostatic, whereas risk signatures are more closely associated with damage-associated microglia. Finally, we identified top protective and risk genes that were also validated in iMGLs. **Conclusion:** Our study identifies microglia-specific protective and risk gene signatures associated with AD risk variants in *PLCG2* and *ABI3*. These signatures are preserved more broadly in AD and associate with its neuropathological severity. Further, they may represent functional microglial transitions that may parallel progression of AD. These findings uncover microglial signatures that may be driving AD neuropathology and microglial dysfunction, and as such may serve as therapeutic candidates.

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Nanosymposium

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

Support: R01AG091534
R01AG086467

Title: Genetic architecture of the human brain glycoproteome implicates TMEM106B and ACE glycosylation in Alzheimer’s disease pathogenesis

Authors: *R. FENG[1], T. (FUNGEN-AD) CONSORTIUM[2], G. WANG[1], H.-U. KLEIN[1]; [1]Columbia Univ., New York, NY; [2]Natl. Inst. on Aging, Bethesda, MD

Abstract: Protein glycosylation is a prevalent post-translational modification that regulates protein folding, trafficking, and function, yet its genetic architecture in the human brain remains poorly characterized. Large-scale quantification of brain glycopeptides with matched genomic

data has been lacking, leaving the contribution of common genetic variation to inter-individual differences in glycosylation undefined. Here, we profiled the glycoproteome of 316 dorsolateral prefrontal cortex samples from the Religious Orders Study and Memory and Aging Project (ROSMAP) using glycopeptide enrichment coupled with LC-MS/MS, quantifying 9,098 glycopeptiforms representing 1,232 glycoproteins, and integrated these measurements with matched whole-genome sequencing and proteomic data.Using Bayesian fine-mapping, we identified 230 glycopeptiforms harboring cis-glycoQTLs. Adjustment for matched protein abundance reduced detected glycoQTLs by 47.0%, demonstrating contributions from both protein-level and glycosylation-specific genetic regulation. Glycosylated peptiforms were more likely to harbor QTLs than glycated peptiforms, and high-mannose glycoforms showed the strongest enrichment for genetic effects, implicating preferential regulation of early glycosylation states established in the endoplasmic reticulum. GlycoQTL variants were enriched in regulatory and open chromatin regions across major brain cell types and showed significant heritability enrichment for Alzheimer's disease (AD) and Parkinson's disease.Glycoproteome-wide association analyses integrating glycoQTLs with AD genome-wide association studies identified 44 AD-associated glycopeptiforms across 17 proteins. Multi-context colocalization and Mendelian randomization prioritized several candidates, including TMEM106B and ACE. At TMEM106B, AD-associated variants colocalized with multiple high-mannose glycoforms at N183 and with protein abundance, implicating site-specific glycosylation in lysosomal pathways linked to neurodegeneration. At ACE, distinct glycoforms exhibited opposing allelic effects at the same AD-associated locus, indicating glycoform-specific functional consequences.These results establish the first large-scale map of glycoQTLs in the human brain and demonstrate that genetically regulated protein glycosylation represents a molecular layer linking genetic variation to AD risk.

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Nanosymposium

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Presentation Number: NANO12.06

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

Support: NIH Grant AG054345

Title: Multi-omic characterization of brain and biofluid responses to aducanumab and verubecestat in an amyloid mouse model

Authors: *G. W. CARTER[1], R. PANDEY[2], S.-P. WILLIAMS[3], D. DUONG[4], P. R. TERRITO[6], N. T. SEYFRIED[5], S. J. SUKOFF RIZZO[7];
[1]Univ. of Arizona, Tucson, AZ; [2]The Jackson Lab., Bar Harbor, ME; [3]Aging Inst., Univ. of Pittsburgh, Pittsburgh, PA; [5]Human Genet., [4]Emory Univ., Atlanta, GA; [6]Med., Indiana Univ.

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Abstract: The advent of anti-amyloid therapies has generated interest in their broader pharmacodynamic effects. Rigorous preclinical studies, including pharmacogenomic assays of brain and biofluids, are warranted to assess treatment effects. The MODEL-AD Consortium has created comprehensive workflows for multi-omic preclinical studies in mice. We treated amyloidogenic 5XFAD mice with vehicle, murinized aducanumab, and immunoglobulin controls and performed transcriptomic (with bulk RNA-seq) and proteomic (with tandem mass tag mass spectrometry and Alamar NULISA) on homogenized brain tissue, plasma, and cerebrospinal fluid. We also tested the BACE inhibitor verubecestat following the same approach. We detected beneficial reversal of multiple protein and gene expression signatures associated with the amyloidogenic 5xFAD transgene. Notably, for both treatments we observed decrease in matrisome proteins consistent with amyloid clearance including Mdk, Smoc1, Apoe, and App, all of which were increased in the presence of amyloid. However, we also observed multiple off target effects in brain and plasma from both treatments, consistent with adverse physiological effects. Finally, we note the aducanumab response was largely similar to treatment with the immunoglobulin control. These results showcase the utility of pharmacogenomic approaches in preclinical animal testing of candidate therapeutics, and highlight the broad and often adverse molecular consequences of candidate anti-amyloid treatments.

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Nanosymposium

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

Title: ADAM/ADAMTS-family plasma signals and parahippocampal MRI context in incident dementia risk in UK Biobank

Authors: *S. YANG;
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Abstract: Blood-based proteomic signals may reveal systemic pathways linked to dementia vulnerability, but their relationship to brain structure remains uncertain. We examined ADAM/ADAMTS-family proteins emerging from a technically bounded UK Biobank Olink plasma-proteomic workflow and their exploratory medial-temporal MRI context. Participants were humans with baseline instance-0 Olink measurements and linked incident all-cause dementia outcomes. The protein-phenotype cohort included 52,948 participants and 914 incident dementia events over a median 15.75 years of follow-up. Single-protein Cox models adjusted for

age, age squared, sex, and PC1-PC10 screened a pre-outcome 50-analyte working panel with FDR correction restricted to that panel. ADAM15, ADAMTS16, and ADAMTS8 were FDR-supported and retained, together with ACE2 and ACY1, in a five-protein risk-enrichment score. In 48,456 complete cases, the standardized score was associated with incident all-cause dementia (HR per SD 1.3367, 95% CI 1.2513-1.4279; P=7.07x10^-18) and remained stable after 2- and 5-year lag exclusions. A post hoc screen across all 2,923 accessible baseline Olink analytes retained FDR<0.05 support for all five score proteins without refitting the score. Exploratory MRI analyses did not identify a score-level correlate across eight medial-temporal targets. ADAMTS8 showed one hypothesis-generating association with left parahippocampal gray-white contrast (N=1,337; beta=0.0778; P=0.0039; q=0.0312). These results support ADAM/ADAMTS-family plasma signals as human dementia-risk correlates with limited parahippocampal context, but not as Alzheimer disease-specific or clinically ready biomarkers. External replication and disease-specific validation are required.

Disclosures: S. Yang: None.

Nanosymposium

NANO12: Alzheimer's Disease: Omics

Location: WCC Rm 144

Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO12.08

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

Support: NIH Grant GR053242

Title: Molecular characterization with spatial resolution of the human middle temporal gyrus in Alzheimer’s disease and LATE co-pathology

Authors: *M. R. VALENTINE, E. E. SCHNEIDEREIT, C. REICHEL, A. WILSON, M. DAMODARASAMY, J. E. YOUNG, C. S. LATIMER;
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia, defined pathologically by extracellular amyloid plaques and intraneuronal tangles of hyperphosphorylated tau. AD frequently co-occurs with other neuropathologies; over 50% of AD cases exhibit TDP-43 pathology, wherein TDP-43 mislocalizes from the nucleus to the cytoplasm and forms insoluble aggregates. The TDP-43 pathology typically associated with AD is termed limbic-predominant age-related TDP-43 encephalopathy (LATE), and it progresses neuropathologically from the amygdala to the hippocampus and ultimately to the neocortex. Combined AD+LATE neuropathology is associated with more severe cognitive impairment than either pathology alone. Despite the prevalence and clinical relevance of AD+LATE co-pathology, the molecular interactions between these pathologies remain poorly understood, although clues may lie in the genetics of AD risk. SORL1 is an established AD risk gene encoding an endosomal sorting receptor critical for amyloid precursor protein trafficking.

Notably, non-coding SORL1 variants are genetically associated with LATE neuropathologic change (LATE-NC), and all autopsy-confirmed carriers of a pathogenic SORL1 missense variant (R953C) in a multigenerational family had comorbid LATE-NC, implicating SORL1 dysfunction in TDP-43 pathobiology. These genetic observations suggest SORL1-mediated endosomal dysfunction as a potential molecular bridge between AD and LATE pathology, yet the downstream transcriptomic and proteomic consequences in human brain tissue remain uncharacterized. The middle temporal gyrus (MTG) is vulnerable to both AD and LATE neuropathology, making it an ideal region to study their convergence. Here we use spatial-omics approaches, enabling disease-associated molecular changes to be resolved at cellular and regional resolution, to characterize the MTG across donors with sporadic AD only (n=4), sporadic AD+LATE (n=4), AD+LATE carrying a familial SORL1 missense variant (n=6), and controls (n=2). Brain tissue from the University of Washington BioRepository and Integrated Neuropathology (BRaIN) laboratory first underwent extensive neuropathological evaluation, including pTDP-43 (S409/410) immunohistochemistry. We then used spatial molecular profiling to identify disease-associated gene and protein expression changes across these groups. These data illuminate the molecular pathways underlying AD and LATE co-pathology burden, clarify whether SORL1 dysfunction shapes the co-pathology landscape, and provide a foundation for large-scale multi-omic studies across brain regions susceptible to AD and LATE progression.

Disclosures: M.R. Valentine: None. **E.E. Schneidereit:** None. **C. Reichel:** None. **A. Wilson:** None. **M. Damodarasamy:** None. **J.E. Young:** None. **C.S. Latimer:** None.

Nanosymposium

NANO12: Alzheimer's Disease: Omics

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Time: Sunday, November 15, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO12.09

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

Support: National Institute on Aging grants 1RF1AG071683 (to V.S.)

Title: Spatial and molecular heterogeneity of human oligodendrocytes shapes brain microenvironment in Alzheimer's disease

Authors: *S. DAS[1], V. SWARUP[2];
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Abstract: Oligodendrocytes are increasingly implicated in Alzheimer's disease (AD) pathophysiology, yet their molecular heterogeneity across brain regions and matter compartments remains poorly characterized. Using 288 postmortem brain sections from 72 individuals spanning control, early AD, and late-stage AD, with gray and white matter dissected separately from prefrontal cortex (PFC) and temporal cortex (TCX), we present one of the most comprehensive compartment-resolved oligodendrocyte landscape of the human brain.To map

oligodendrocyte heterogeneity across transcriptomic, epigenomic, and proteomic levels, we leveraged an integrative multi-modal framework combining snRNA-seq, Paired-Tag, Xenium spatial transcriptomics, and proteomics — generating one of the largest human oligodendrocyte datasets to date and revealing previously uncharacterized subtypes, including disease-adaptive oligodendrocytes with distinct molecular landscapes. Oligodendrocytes exhibited significant matter-compartment specificity, with white matter and gray matter OLG populations displaying divergent transcriptional identities and disease-associated responses. Our studies identified temporal cortex white matter OLGs as the most vulnerable population in both AD and age matched control individuals. This vulnerability was characterized by dysregulation of myelination, epigenetic inactivation, immune hyperreactivity and sever stress-response programs. To assess therapeutic potential, we tested transcriptional reprogramming strategies targeting OLGs in an AD mouse model. Early-life intervention significantly reshaped the CNS microenvironment, and modified disease trajectory, suggesting a window of opportunity for OLG-directed therapeutic strategies.

Disclosures: S. Das: None. **V. Swarup:** None.

Nanosymposium

NANO13: Pain and Itch

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Presentation Number: NANO13.01

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH NIDDK: 4R00DK142197-02

Title: Tau Phosphorylation in the Sensory Neurons of Mice with Diabetic Neuropathy.

Authors: *C. N. AKANIRU-MADUAKO[1,2], H. M. HAYES[2], B. V. PINHEIRO[2], K. CALINDAS[2], A. J. SHEPHERD[3], J. M. NICHOLS[2];
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Abstract: ABSTRACT Type 1 Diabetes Mellitus (T1DM) stems from insulin deficiency, with roughly 50% of patients developing diabetic neuropathy (DN). Approximately 30% of these individuals progress to painful diabetic neuropathy (PDN), presenting with chronic pain, hyperalgesia, and allodynia. While tau hyperphosphorylation and tangles are well-documented in central nervous system (CNS) disorders like Alzheimer's disease, the role of tau in the peripheral nervous system (PNS) associated disorders and PDN remains unelucidated. Unlike CNS neurons, peripheral neurons rely on "Big Tau", a high-molecular-weight isoform featuring a unique ~250-amino-acid domain encoded by exon 4a to the projection domain. This domain acts as a physical spacer between microtubule tracks. Factors like metabolic stress can induce pathological destabilization of these tracks; however, the precise mechanistic role of tau in PDN

pathogenesis is unknown. We therefore hypothesize that insulin deficiency increases aberrant tau phosphorylation, which contributes to axonal instability and neurodegeneration in PDN. In this study, we investigated the association of tau phosphorylation with PDN development. T1DM was induced in mice using streptozotocin (STZ), and behavioral assays were performed to detect thermal and mechanical sensitivity at 4 and 9 weeks post induction. Dorsal root ganglia (DRG) and sciatic nerve tissues were harvested for comprehensive immunohistochemistry and western blotting analysis. For histological samples, linear regression and k-means clustering were utilized to quantify and map signal colocalization within specific neuronal subtypes. Our results show an increase in tau phosphorylation in the peripheral nerves of diabetic mice, as compared to vehicle treated mice. This molecular change was accompanied by increased mechanical sensitivity and no change in thermal sensitivity. Furthermore, linear regression and k-means clustering showed a high spatial overlap of tau-phosphorylation within $CGRP^{+}$ neurons. Collectively, these results reveal a novel consequence of decreased insulin signaling on peripheral nerve structural integrity, highlighting the detrimental impact of insulin deficiency on tau homeostasis and its potential role as a key driver of diabetic neurodegeneration and PDN.

Disclosures: C.N. Akaniru-Maduako: None. **H.M. Hayes:** None. **B.V. Pinheiro:** None. **K. Calindas:** None. **A.J. Shepherd:** None. **J.M. Nichols:** None.

Nanosymposium

NANO13: Pain and Itch

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Time: Sunday, November 15, 2026, 1:00 PM - 3:45 PM

Presentation Number: NANO13.02

Topic: E.01. Somatosensation – Pain and Itch

Support: R01DC022946

Title: Lingual Itch Sensation: Single Cell Transcriptomics, Genetic Labelling, and Functional Imaging

Authors: *A. FARIDIESFANJNAI[1], S. CHUNG[1], C. OH[1], M. GRADWELL[2], M. KISSNER[3], J. C. DE NOOIJ[4], Y. MOAYEDI[1];
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Abstract: Itch is an unpleasant sensation triggered by different pruritogens and mechanical stimuli that are detected by distinct dedicated neuronal populations. While cutaneous pruritus is common, tongue pruritus is rare. We sought to investigate whether there is a neurobiological basis for the infrequency. We used RNA-seq, integrated analytical methods, genetic labeling, and functional imaging for molecular and functional identification of tongue innervated populations. Tongues of 6 male and 6 female C57BL/6J mice were injected with a fluorescent retrograde

tracer, and then labelled trigeminal ganglion neurons were sorted for PLATE-Seq. Data were analyzed in Seurat through four steps: preprocessing, CCA-based integration with published trigeminal atlases, clustering, and visualization. Cluster markers were validated histologically. We identified ten clusters of tongue-innervating trigeminal neurons including peptidergic and non-peptidergic nociceptors, thermoreceptors, pruriceptors, and mechanoreceptors. In the tongue, as in the entire trigeminal system, *MRGPRD*-pruriceptors are present, expressing receptors for β-alanine and cytokines. Surprisingly, we observed that lingual sensory neurons do not include *MRGPRA3* expressing pruriceptors, which transduce chloroquine, cytokines, proteases, histamine, amongst other pruritogens. Consistent with these observations, *in vivo* trigeminal calcium-imaging revealed that the tongue is responsive to β-alanine but not to chloroquine. Moreover, *NPPB* expressing pruriceptors; which express receptors for serotonin, cytokines, histamine, and inflammatory lipids; innervate the tongue but lack receptors for histamine. These findings suggest that lingual neurons lack transduction machinery for major pruritogens including chloroquine and histamine. Our findings suggest that lingual pruritogen transduction is limited. Lingual pruritogen-sensing neurons may be involved in paresthesia (tingling) and acute irritation that alert to oral allergen consumption or flavors.

Disclosures: A. Faridiesfanjnai: None. **S. Chung:** None. **C. Oh:** None. **M. Gradwell:** None. **M. Kissner:** None. **J.C. De Nooij:** None. **Y. Moayedi:** None.

Nanosymposium

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01EY033712 (AGJS)

Title: Chemogenetic Sensitization of Corneal Nociceptors to Model Chronic Pain in the Absence of Tissue Damage

Authors: *D. MOLINA PALACIOS[1], A. SCLAR[2], A. CRUZ RIVERA[1], A. SKORPUT[3]; [1]Dartmouth Col., Hanover, NH; [2]Dartmouth Col., Lebanon, NH; [3]Neurol., Dartmouth Hitchcock Med. Ctr., Lebanon, NH

Abstract: The contribution of neuroimmune interactions to the establishment and maintenance of chronic pain remains an understudied area. Here, we constructed a model of chronic ocular pain by driving nociceptor activation in the absence of tissue damage. As such, transgenic mice that express the hM3Dq Designer Receptor Exclusively Activated by Designer Drugs (DREADD) in a Cre-dependent manner were crossed with Nav1.8-Cre mice that express Cre in peripheral nociceptors to yield hM3Dq/Nav1.8-Cre mice. To model chronic sensitization of ocular nociceptors, we applied the pharmacologically inert DREADD ligand (Compound 21) to both eyes of 12 to14 weeks old hM3Dq/Nav1.8-Cre and genetic controls twice a day for 14 days.

Exploratory behaviors, substance P levels in eyewash, and cFos immunoreactivity in the Trigeminal Nucleus Caudalis (TNc) were measured to quantify sensitization of ocular nociceptors. After a single dose of Compound 21, animals expressing DREADD moved significantly less in the open field test, compared to negative littermates. Moreover, substance P levels in the eyewash of DREADD animals were significantly increased. Further, after a noxious stimulus to the eye (2M NaCl), cFos-staining in the TNc was increased in DREADD animals compared to the control group. Furthermore, compound 21-induced pain-related behavior onset was antagonized by topical application of 2% lidocaine. After 14 days of Compound 21 administration, DREADD mice moved significantly less in the open field test and substance P levels in the eyewash were significantly increased, when compared to the genetic control. Interestingly, tear volume was found to be significantly decreased in DREADD mice. After this chronic administration of Compound 21, animals were given a noxious stimulus to the eye (2M NaCl) 24 hours after the last dose. At this timepoint, cFos-staining in the TNc was elevated in DREADD animals, compared to the control group. Transcriptional changes in the cornea after chronic administration of compound 21 was assessed by RNA sequencing. Gene Set Enrichment Analysis (GSEA) revealed upregulation of chemotaxis, a neuroinflammatory pathway. Together, these findings reveal that our model acutely and chronically sensitizes nociceptors. Moreover, chronic sensitization of nociceptors persists beyond Compound 21 administration and induces neurogenic inflammation in the absence of tissue damage. Thus, this model offers a uniquely advantageous framework to study neuroimmune interactions in chronic pain.

Disclosures: D. Molina Palacios: None. **A. Sclar:** None. **A. Cruz Rivera:** None. **A. Skorput:** None.

Nanosymposium

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Presentation Number: NANO13.04

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant HL173002
NSF 2334697

Title: Regional Differences of Itch Transmission Pathways in Hairy and Glabrous Skin

Authors: *S. WU[1], K. LAWSON[2], R. STEWART[1], S. TANG[3], V. YELLA[1], J. YANG[3], L. HAN[2];
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Abstract: Itch is a common and debilitating sensory experience that can substantially impair quality of life. While itch sensation can originate from any area of the skin, it can be particularly debilitating when occurring on glabrous (non-hairy) skin, such as the palms and soles. Our previous work demonstrated higher itch sensitivity in glabrous skin compared with hairy skin, as

evidenced by the lower optogenetic stimulation thresholds and pruritogen concentrations required to elicit itch-related behaviors. This regional difference in itch sensitivity parallels the distinct morphological organization of MrgprC11^{+} neurons, which mediate itch in both hairy and glabrous skin, supporting a somatotopic mechanism for regional sensory processing. In this study, we aimed to investigate the molecular mechanisms underlying the regional differences in itch transmission. RNA-seq analysis identified distinct transcriptional signatures between itch-sensing neurons innervating hairy and glabrous skin, including differential expression of ion channels and GPCRs, as well as enrichment of genes related to synaptic function, cell-cell communication, and sensory signal transduction. We also performed calcium imaging and found that glabrous skin-innervating sensory neurons exhibit higher sensitivity to pruritogen stimulation. Taken together, these results provide molecular and cellular insights into the mechanisms of the regional differences in itch transmission.

Disclosures: S. Wu: None. **K. Lawson:** None. **R. Stewart:** None. **S. Tang:** None. **V. Yella:** None. **J. Yang:** None. **L. Han:** None.

Nanosymposium

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Presentation Number: NANO13.05

Topic: E.01. Somatosensation – Pain and Itch

Support: Johns Hopkins School of Medicine Neurosurgery Pain Research Institute

Title: Dichotomous alterations in temperature sensation in mice with Hereditary Palmoplantar Keratoderma

Authors: *S. KIM[1], P. JACKSON[2], M. J. CATERINA[1];
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Abstract: Palmoplantar keratodermas (PPK) are a group of rare hereditary skin disorders characterized by abnormal epidermal thickening on the palms of the hands and soles of the feet and, in some but not all cases, debilitating pain. Treating PPK-associated pain poses a challenge due to limited understanding of its underlying molecular mechanisms. Two mouse models, secreted Ly6/uPAR-related protein 1 (Slurp1) knockout mice and Slurp2 knockout mice, recapitulate features of particular human PPK, Mal de Meleda. We have previously reported that both mouse lines display PPK in their paws and exhibit hypersensitivity to mechanical, chemical, and heat stimuli, as well as increased spontaneous pain-like behavior.However, we have found that, in contrast to other stimuli, Slurp knockout mice exhibited longer withdrawal latencies to acute cold stimuli suggesting a cold hyposensitivity phenotype. Also, spontaneous pain-like behaviors in Slurp knockout mice on a non-noxious cold surface were reduced compared to those on a room temperature surface. mRNA levels of various thermal-sensitive ion channels including

TRPV1, TRPM8, TRPC5 and GluK2 glutamate receptors were not significantly altered in Slurp knockout paw-innervating dorsal root ganglia (DRG) compared to wildtype. TRPA1 mRNA was upregulated in the Slurp knockout paw-innervating DRGs. The TRPA1 ion channel is reported to be activated by cold in expression systems, but whether it is activated by cold in neurons and contributes to the sensation of cold pain is controversial. Slurp TRPA1 double knockout mice did not differ from Slurp single knockout mice in responses to acute cold stimuli to their paw.This dichotomy of responses to different thermal stimuli to Slurp knockout mice reveals unappreciated complexity of sensory alterations in Slurp knockout mice and may have implications for understanding and treatment of pain in patients with PPK.

Disclosures: S. Kim: None. **P. Jackson:** None. **M.J. Caterina:** None.

Nanosymposium

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Topic: E.01. Somatosensation – Pain and Itch

Support: Austrian Science Fund I-050870
National Research, Development and Innovation Office, Hungary ANN 136027

Title: Modality-Specific Nociceptor Reprogramming in Inflammatory Pain

Authors: *L. WANG[1], D. ZIMMERMANN[2], I. DRISSI[1], N. HOQUE[1], E. PINTER[3], T. MACHADO[5], A. KECSKES[4], M. KRESS[6], V. DANKE[1], I. NAGY[1];
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Abstract: Inflammatory pain is characterised by enduring tenderness (mechanical allodynia) and burning pain (heat hyperalgesia), which are driven by post-translational modifications and transcriptional alterations in more than 10 transcriptionally and functionally defined types of primary sensory neurons responding to noxious stimuli (nociceptors). Our recent work has revealed that heat hyperalgesia, but not mechanical allodynia, depends on the emergence of a novel nociceptor group within the PEP1/CALCA-SSTR2 cluster of nociceptors. To further characterise the cellular segregation of the two main inflammatory pain modalities, spatial transcriptomics (Visium HD, 10x Genomics) on the lumbar 4 (L4) dorsal root ganglion followed by bioinformatics analysis was performed using the Complete Freund's Adjuvant (CFA)-induced inflammatory pain model in adult mice. UMAPs in naïve (794 neurons) and inflamed conditions (877 neurons) indicated expansion of PEP1, NP1 and cLTMR clusters. Quantification confirmed this expansion and revealed reduction in the relative number of proprioceptive and AbLTMR neurons. The re-arrangement of clustering was based on CFA-induced upregulation of 197, and

downregulation of 69, genes (|log2FC| > 0.25, adjusted p < 0.05) among the 10,468 detected of the 19,454 genes targeted by the Visium HD mouse probe set (v1.0). One of the three annotated major GO biological functions included modules of heat or mechanical stimulus detection in pain. Visualisation of heat and mechanical pain-associated gene sets showed clear cellular segregation; while PEP1 cells were enriched with heat pain-associated genes, mechanical pain-associated genes were mainly present within the NP1 cluster, but some neurons in the NP2-3 and cLTMR clusters also expressed those genes. These findings demonstrated that inflammation induces profound transcriptional alterations leading to reprogramming that extends beyond conventional somatosensory functions in primary sensory neuron. Crucially, the reprogramming was highly cluster specific, which shows that the gene expression profile - function correlation demonstrated in the naïve condition is preserved in pathology. Collectively, these findings support a modality-specific model of inflammatory pain and help understanding of nociceptive mechanisms in primary sensory neurons better.

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Nanosymposium

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5K01DA058543

Title: Inhibitory RVM neurons coordinate pain and breathing: sex-dependent analgesia and conserved respiratory depression

Authors: *R. S. PHILLIPS;
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Abstract: The rostral ventromedial medulla (RVM) is the primary output node of the descending pain modulatory network and an essential site for opioid analgesia. The RVM also exerts bidirectional control over respiration and may therefore contribute to opioid-induced respiratory depression (OIRD). However, how genetically defined RVM populations shape both pain and breathing remains poorly understood. Here, we examined this by optogenetically activating inhibitory (VGAT-expressing) RVM neurons in awake and lightly anesthetized male and female mice, combining whole-body plethysmography, retrograde tracing, and thermal nociceptive testing (Hargreaves). Activation of these neurons depressed breathing, an effect enhanced by light anesthesia and, at times, resulting in prolonged apneas. Histological analysis and retrograde tracing confirmed monosynaptic RVM projections to the ventral respiratory column, in the region of the preBötzinger complex and nucleus ambiguus, providing an anatomical substrate for

respiratory control. Notably, the same activation produced profound analgesia in males that was markedly attenuated or absent in females. Conversely, noxious thermal stimulation modulated respiratory output, indicating reciprocal coupling between nociceptive and respiratory control. Together, these findings show that inhibitory RVM neurons coordinate pain and breathing. Their respiratory effects are conserved across sexes whereas their analgesic effects are strongly male-biased, with implications for sex differences in pain management, opioid analgesia, and OIRD risk.

Disclosures: R.S. Phillips: None.

Nanosymposium

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 1R01AG093283
NIH Grant R35NS111643

Title: Activity-dependent degeneration of spinal circuits drives somatosensory dysfunction in aging and peripheral neuropathy

Authors: *D. ACTON, S. PIMPINELLA, M. D. GOULDING;
Mol. Neurobio. Lab., Salk Inst., La Jolla, CA

Abstract: The mechanisms that drive somatosensory dysfunction during aging remain poorly understood. Chronic pain and itch conditions severely impact quality of life in elderly populations, while the loss of touch sensitivity that occurs during normal aging degrades motor function and increases fall risk. We show that the somatosensory system fails at multiple levels during aging: Following the degeneration of touch-sensitive Merkel cells in the skin, we observe the loss of interneurons in the spinal dorsal horn (DH) that transmit and modulate somatosensory information. Although both excitatory and inhibitory neurons are reduced in number following the loss of input from touch receptors, some molecularly defined populations are highly vulnerable to activity- and age-dependent degeneration, while others are resilient. The consequent reorganization of DH somatosensory circuits disrupts the transmission and modulation of sensory information, resulting in the chronic itch and pain phenotypes and reduced motor ability observed in aging. We show that the degeneration of neuropeptide Y (NPY)+ DH interneurons following the loss of Merkel cell signaling results in reduced inhibitory NPY-Y1 receptor signaling and disinhibition of the spinal pathways that transmit mechanical itch and inflammatory pain. Notably, glutamatergic neurons expressing Y1 are resilient to the loss of Merkel cells, and Y1 activation suppresses pain and itch in aged mice, suggesting Y1 agonism as a potential therapeutic strategy.
Our finding that DH neurons degenerate following the loss of peripheral mechanosensory drive

raises the possibility that the same mechanism operates across conditions characterized by impaired afferent input to the DH, including peripheral neuropathies. In support of this, we find a striking reduction in DH neuron number in a mouse model of chemotherapy-induced peripheral neuropathy (CIPN). As in aging, NPY+ neurons are significantly reduced in number following cisplatin treatment, resulting in enduring pain and itch hypersensitivity, as well as persistent cold allodynia. These data establish activity-dependent DH neurodegeneration as a broadly operative mechanism of sensory dysfunction, with implications for therapeutic approaches across a range of conditions.

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Nanosymposium

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Lafitte Undergraduate Research Fund 3980629

Title: Machine learning-based behavioral mapping for spontaneous-pain in freely moving mice

Authors: *R. LI[1], S. SONG[1], R. GUO[2], R.-R. JI[3];
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Abstract: Spontaneous pain in mice is difficult to quantify because manual observations remain labor-intensive and current machine learning approaches such as grimace scale and black-box assay are supervised and category-limited. We tested whether inflammatory spontaneous pain alters natural whole-body behavior in a manner detectable across a shared 3D behavioral atlas based on coordinates of 21 joints. We further examined whether the generated atlas distinguishes specific behavioral types, which are modulated by effective analgesic treatments . Three-camera markerless tracking and reprojection-trained 3D pose reconstruction were used to summarize distinct behavioral patterns into one-second windows, which were then embedded into unsupervised atlas. The identified microregions were summarized into 16 atlas macroregion groups from a lower-resolution partition of the fixed atlas. After microregions were defined, representative frames, short video windows, and aligned pose traces were extracted for selected microregions and reviewed with mouse-level cohort summaries masked. We identified four syllable sets that are associated with spontaneous pain, including guarding, licking, flicking, and flinch/shake behaviors following intraplantar injection of capsaicin or formalin in mice. In addition to speed, DANNCE-derived 3D kinematic signatures further detected the amplitudes of

paw-lift. We found that matched analgesic interventions such as lidocaine and protectin DX (PDX), a pro-resolution lipid mediator, reduced reactive atlas occupancy , showing inhibitory effects of lidocaine in the formalin model and PDX in the capsaicin model. Post hoc exact-test/downsampling analysis revealed that high-signal atlas endpoints could be analyzed with a small sample size (n=4 mice). These results indicate that unsupervised 3D and whole-body behavioral mapping can reliably assess multiple spontaneous pain phenotypes, which are highly sensitive to analgesic treatments. Future studies will extend to different models and define novel behavioral patterns that are associated with acute and chronic pain.

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Nanosymposium

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Presentation Number: NANO13.10

Topic: E.01. Somatosensation – Pain and Itch

Title: Reversing central maladaptive plasticity with vagus nerve stimulation to treat chronic neuropathic pain

Authors: *C. L. NEIFERT[1,2], T. T. DANAPHONGSE[2], M. P. KILGARD[3,2], S. A. HAYS[1,2];
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Abstract: Chronic neuropathic pain is a debilitating condition that arises from damage to and maladaptive rewiring of the nervous system. As such, neuroplasticity has become a prominent potential avenue for understanding and modulating pain in these circuits. Vagus nerve stimulation (VNS), when paired with rehabilitation, has been well documented to induce plasticity in other motor and sensory circuits and improve functional outcomes following neurological injury. While previously used in models of hyposensitivity, this technique holds promise for the treatment of chronic pain and associated nociceptive hypersensitivity. Previous studies show that VNS and pain engage similar neuromodulatory pathways and thus may interact. The goal of this experimental study is two-fold: first, to examine how VNS-driven cortical plasticity is affected by chronic neuropathic pain, and second to develop a therapeutic strategy that combines VNS, pharmacology, and somatosensory therapy to treat chronic pain. Two original experiments were performed: chronic pain was induced via radial nerve injury (RNI) in two cohorts of rats, and in one cohort, plasticity was evaluated by assessing cortical changes after a trained motor task was paired with VNS and pharmacology. In the second cohort, these findings were applied to develop a therapy for pain rehabilitation and was administered to rats, consisting of VNS, one of the previous drugs, and a paired tactile stimulus.
Our results show that RNI is effective at driving long-lasting neuropathic allodynia. When delivered during a motor task, Moderate VNS effectively increases cortical plasticity in health rats compared to sham. However in rats with RNI, Moderate VNS does not increase plasticity

compared to sham nor to healthy rats. RNI rats that receive propranolol (β-adrenergic receptor blocker) with Moderate VNS do experience enhanced plasticity. So do rats with suzetrigine (peripheral nociceptor inhibitor) and Moderate VNS, implicating the overactivation of the noradrenergic system resulting from nociception. After VNS-paired tactile therapy, Moderate VNS with suzetrigine has been successful at driving increased withdraw thresholds, with improvements lasting over a month after rehabilitation. Propranolol however was not effective at increasing withdrawal threshold, suggesting that noradrenergic modulation during VNS alone is not sufficient for driving improved somatosensation. This study explored the neurological mechanisms underpinning pain and VNS-driven plasticity, and lays the groundwork for developing a fundamentally novel, promising approach toward a long-lasting rehabilitation of post-injury chronic pain.

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Nanosymposium

NANO13: Pain and Itch

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Time: Sunday, November 15, 2026, 1:00 PM - 3:45 PM

Presentation Number: NANO13.11

Topic: E.01. Somatosensation – Pain and Itch

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Title: Pain is not a unified process: Modality-specific adaptation shapes neural dynamic and representations of sustained noxious stimulation

Authors: *M. ZHANG[1,3,4], Y. KONG[2,4,5];
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Abstract: Pain perception exhibits dynamic variability in response to noxious stimuli, yet it remains unclear whether adaptation mechanisms generalize across nociceptive modalities. In this study, we investigated modality-specific perceptual and neural dynamics during noxious stimulation. Across six experiments, healthy participants received heat, pressure, or electrical stimulation. Behavioral analyses quantified sensitization and habituation, while functional MRI characterized temporal changes in brain activity during 30-s continuous stimulation. Repeated stimulation revealed distinct adaptation profiles: heat pain remained relatively stable, pressure

pain consistently sensitized, and electrical stimulation showed intensity-dependent effects. During sustained stimulation, heat exhibited an early sensitization-to-habituation transition, pressure showed persistent sensitization, and electrical stimulation demonstrated robust habituation. These perceptual trajectories were accompanied by divergent neural dynamics, with pressure pain eliciting increasing activity in sensorimotor and salience-related regions and electrical pain showing progressive attenuation in overlapping cortical networks. Cross-temporal MVPA revealed stable neural representations for pressure pain but substantial temporal reorganization of electrical pain representations. RSA localized these representational changes to sensorimotor and frontal regions. Neurochemical decoding further demonstrated dynamic serotonergic and GABAergic correspondence profiles for electrical pain, whereas pressure pain showed comparatively stable neurochemical organization. These findings demonstrate that pain adaptation is highly modality dependent, involving distinct perceptual trajectories, neural dynamics, representational structures, and neurochemical architectures. The results challenge unified models of pain adaptation and provide new insights into the temporal organization of sustained pain.

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Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO14.01

Topic: H.08. Drugs of Abuse and Addiction

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Title: Trigeminal circuits dictate innate rejection thresholds for ethanol through oral chemesthesis

Authors: *S. MUKERJEE, R. LARIVEE, Y. QUAN, S. PIERCE, D. B. COHEN, Y. HAN, V. MAHAJAN, A. BHATT, E. KARTHIKEYAN, K. SONG, A. BROWN, Z. FARAHBAKHSH, K. R. ERICKSON, C. A. SICILIANO;
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Abstract: Alcohol, specifically ethanol (EtOH), is a noxious substance that should be rejected as a toxin due to its burning/tingling sensation. Despite that, animals across species readily consume EtOH. Its central pharmacological effects are reinforcing, but the neural mechanisms

driving initial palatability are unknown. Heavy drinkers may use EtOH substitutes like mouthwash or gasoline when an alcoholic beverage is inaccessible, suggesting a chronic disruption in innate chemical defense systems responsible for oral rejection of toxins. Here we identify the circuit responsible for oro-sensory detection of a toxin to manipulate the threshold of rejection. EtOH's complex flavor profile includes pronounced irritant/burning sensations, termed oral chemesthesis, which become dominant at high concentrations. Following oral stimulation with palatable (15%) versus chemesthetic (50%) concentrations of ethanol, whole-brain cFOS mapping revealed chemesthetic-selective activation of multiple sub-nuclei in the spinal trigeminal nucleus. The trigeminal ganglion (TG) in the peripheral nervous system is a strong candidate for projecting to this brain region, mainly TRPV1+TG neurons, as they code the burning oro-sensation of capsaicin (chili pepper). Immunofluorescence in primary cultures showed that 72% of TG neurons expressing TRPV1 receptors co-express vesicular glutamate transporter 2 (VGLUT2), indicating they are excitatory. To trace TRPV1+ TG neuron projections, AAV-hSyn-DIO-mCherry was injected into the TG of a TRPV1-cre mouse. The whole head was cleared and imaged to preserve intact peripheral circuits. Light sheet imaging revealed anatomical projections to both the tongue and the spinal trigeminal nucleus caudalis (TNC) within the brainstem. These projections overlapped with the observed cFOS activity, indicating both anatomical and functional relevance of TNC. It confirms that the TRPV1+ TG neurons are centrally positioned to relay sensory information from tongue to brainstem. Stereotaxically-targeted pharmacogenetic lesions of TRPV1+ TG neurons produced a robust blunting of oral rejection to capsaicin, and resulted in preference for low doses of EtOH and augmented rejection thresholds for its higher concentrations. Endoscopic multiphoton through-brain imaging of single cell calcium dynamics in TG during consumption of tastants and chemesthetics revealed EtOH-selective, concentration-dependent sensory coding. Together, we anatomically and functionally describe a peripheral-central circuit involved in mammalian chemosensation, which controls palatability of EtOH thereby altering motivation and consumption.

Disclosures: S. Mukerjee: None. **R. Larivee:** None. **Y. Quan:** None. **S. Pierce:** None. **D.B. Cohen:** None. **V. Mahajan:** None. **A. Bhatt:** None. **E. Karthikeyan:** None. **K. Song:** None. **A. Brown:** None. **Z. Farahbakhsh:** None. **K.R. Erickson:** None. **C.A. Siciliano:** None.

Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO14.02

Topic: H.08. Drugs of Abuse and Addiction

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Title: Alcohol cues drive persistent medium spiny neuron signaling in the nucleus accumbens

Authors: *H. YOON[1], H. ELAM[2], M. Z. LEONARD[2], M. CHEVEE[1], E. S. CALIPARI[2]; [2]Pharmacol., [1]Vanderbilt Univ., Nashville, TN

Abstract: Cue-reinforcer associations strengthen with experience, increasing motivated behaviors. Alcohol, as a reinforcer, hijacks these associations, promoting maladaptive alcohol use. The nucleus accumbens (NAc) integrates stimuli-related information and mediates cue-driven motivation, making it a key site of alcohol-induced dysregulation. While D1- and D2-receptor-expressing medium spiny neurons (MSNs) play complementary roles in associative learning, their specific contributions to alcohol-related cue processing remain unclear. Here, we examined D2 MSN activity with Cre-dependent GCaMP8m in A2a-cre mice (n=10 males, n=7 females) during cue-reinforcer learning and outcome updating for alcohol and sucrose. Using fiber photometry, we recorded calcium dynamics time-locked to cues, lever presses, and drinking bouts during FR1 self-administration. Throughout learning, D2 MSN activity increased at cue onset and decreased during licking for both reinforcers ($p<0.05$). Using generalized linear models, we found that sucrose cue-evoked D2 MSN activity predicted both lever pressing and licking. In contrast, ethanol cue-evoked activity predicted licking only. Optogenetic inhibition of D2 MSNs at the ethanol cue reduced licking relative to eYFP controls without affecting lever pressing ($p<0.05$). When reinforcers were omitted, D2-MSN cue-evoked activity updated for sucrose but failed to update for ethanol, even within the same animal, indicating a stimulus-specific disruption in activity updating rather than a global deficit in D2 MSN function. Using one-photon imaging with miniature head-mounted microendoscopes to record neural activity at the cellular level, we found that individual D2 MSNs exhibited reinforcer-specific tuning, with distinct subpopulations preferentially encoding ethanol vs. sucrose licks. Additionally, over learning, ethanol-cue-encoding D2 MSNs became increasingly stable on trials where drinking did not occur, suggesting cue-evoked activity persists independent of ethanol drinking. This shift was not observed for sucrose. Together, these findings show that D2 MSN responses to ethanol-cue develop during learning, fail to extinguish upon reinforcer omission, and are carried by functionally distinct subpopulations. This highlights a circuit-level mechanism through which alcohol may promote rigid, cue-driven consumption.

Disclosures: H. Yoon: None. **H. Elam:** None. **M.Z. Leonard:** None. **M. Chevee:** None. **E.S. Calipari:** None.

Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO14.03

Topic: H.08. Drugs of Abuse and Addiction

Title: Sex-specific differences in alcohol intake and withdrawal in mice lacking the habenular PKA subunit RIIα suggest changes in reward appraisal and negative valence

Authors: M. BLOYD[1], V. K. CHITTAJALLU[2], A. VLACHOS[3], D. ABEBE[3], A. CACCAVANO[4], E. LESKO[6], N. EISEN[5], G. A. VARGISH[7], C. J. MCBAIN[8], ***E. LONDON**[5]; [1]Med. Univ. of South Carolina, Charleston, SC; [2]Lab. of Cell. and Synaptic Neurophysiol., NICHD, NIH, Bethesda, MD; [3]NICHD/NIH, Bethesda, MD; [4]Section on Cell. and Synaptic Physiol., NIH/NICHD, Washington, DC; [5]NIH/NICHD, Bethesda, MD; [7]Section on Cell. and Synaptic Physiol., [6]NICHD, Bethesda, MD; [8]Lab. Cell/Molec Neurosci, NIH, Bethesda, MD

Abstract: Mice lacking *Prkar2a*, which encodes the PKA regulatory subunit RIIα, show altered reward-related behaviors, including reduced intake of palatable food, sucrose and increased voluntary running. These phenotypic changes are driven by disrupted PKA signaling in the medial habenula (mHb), where RIIα is highly and specifically expressed. Because the mHb-interpeduncular pathway regulates midbrain monoamines, negative affect, and is involved in the cycle of addiction/withdrawal/relapse, we hypothesized that alcohol consumption and withdrawal would be impacted by these mHb signaling defects. Using two-bottle choice, drinking-in-the-dark (DID), chronic intermittent access, and acute alcohol exposure and withdrawal assays, we evaluated preference, sensitivity, and intake, and investigated acute alcohol-evoked habenular signaling. Phosphorylation in PKA-dependent and independent pathways in mHb, and rate-limiting monoamine synthesis enzyme levels in regions downstream of mHb after chronic exposure are under investigation. Given known sex differences in PKA-related phenotypes and addiction-relevant behaviors, we examined both sexes. Although ethanol sensitivity did not differ by sex or genotype, mice exhibited different genotype- and sex-specific alcohol intake patterns depending on paradigm and duration of access. During DID with 4h access to 10% ethanol only, RIIα$^{-/-}$ (KO) females consumed and escalated alcohol intake more than WT females, whereas KO males did not escalate intake as WT males did. Alternatively, during repeated 24h access to both 10% ethanol and water, KO females drank less and had decreased preference than WT females, while KO males drank more and had increased preference compared to WT males. Home cage activity monitoring during 2-bottle access and acute withdrawal revealed phasic activity differences in females, indicating sex- and genotype-dependent differences in drinking patterns and negative affect. As expected, phosphorylated CREB (Ser133) was decreased in mHb of KO mice and we identified genotype- and sex-specific alterations in tyrosine hydroxylase and other monoamine regulatory protein levels that may inform about the divergent behavioral phenotypes. Single-nucleus RNA-seq of untreated WT and KO habenula supports links between mHb PKA and alcohol-related signaling pathways. Functional enrichment analyses revealed significant differences in alcoholism susceptibility and reward signaling pathways. These findings highlight a role for habenular PKA signaling and the RIIα subunit in shaping ethanol intake patterns and preference.

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Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

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Presentation Number: NANO14.04

Topic: H.08. Drugs of Abuse and Addiction

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NIH R01AA027213

Title: Inactivation and Neural Dynamics of Orbitofrontal Cortex Activity during Punished Alcohol Seeking and Consumption

Authors: *S. SOTO, K. CHAN, I. HE, S. SENGUPTA, P. H. JANAK;
Johns Hopkins Univ., Baltimore, MD

Abstract: Evidence suggests that orbitofrontal cortex (OFC) is a critical substrate for decision-making, encoding outcomes and the cues associated with them. However, it remains unclear how OFC supports decision making for alcohol (EtOH) rewards when EtOH seeking is associated with punishment. Here, we combined *in vivo* intracranial pharmacological manipulation and 1-photon calcium imaging to probe OFC function during self-administration and punished seeking for EtOH. Long Evans rats first received homecage intermittent access to EtOH (15% v/v), followed by instrumental training for EtOH (~6 wks) in which discrete trials were initiated by a 10s cue (houselight or white noise) followed by the insertion of the EtOH-seeking lever, with EtOH rewards (20%; 0.1 mL) delivered after 2 lever press responses. After this training, rats underwent 14 punishment sessions wherein trials were initiated with a new 10s cue (white noise or houselight) and lever presses for EtOH were paired with aversive footshock. Finally, rats were tested on a cued conflict task wherein trials initiated with either the unpunished discriminative cue (0% shock probability), punished discriminative cue (100% shock probability), or both cues concurrently (50% shock probability), during which lever pressing for EtOH was measured. During self-administration, we recorded OFC CAMKII-GCAMP6s activity via 1-photon imaging in freely moving rats (n = 3 M, ~185 cells). Neuronal activity across trial events was statistically compared to a null distribution of circularly shifted data to identify populations of neurons significantly modulated by trial events. Through this analysis, we identified small cell populations significantly modulated by trial cues, such as the trial initiation cue (~8% of recorded population) and lever insertion cue (~12% of population). In contrast, we identified large cell populations modulated during the anticipatory time bins prior to the lever press (~37% of population) and during EtOH consumption (~60% of population). To assess the functional role of the OFC in our cued conflict task, Long Evans rats (n=5, 3M/2F) received bilateral OFC microinfusions of either muscimol/baclofen or saline prior to testing. OFC inactivation suppressed EtOH seeking during cued conflict (RM ANOVA, $F(1,4) = 13.23$, $p < 0.05$) but had no effect on free intake of EtOH in control sessions ($p > .05$). These findings suggest that the OFC is differentially recruited during decision making for EtOH rewards when punishment risk is cued compared to when EtOH is freely available to drink, supporting the hypothesis that the OFC is a critical substrate for decision-making under punishment.

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Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

Location: WCC Rm 146C

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Topic: H.08. Drugs of Abuse and Addiction

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enter for Advanced Light Microscopy and Nanoscopy (CALMN) at the University of Rochester Medical Center for their guidance, instrument support, and technical assistance.

Title: Microstructural and Cellular Fingerprints of Chronic Alcohol Use in Mice: Insights from Multiparametric Diffusion MRI and Light Sheet Microscopy

Authors: *M. C. MARRERO[1], T. NEUBERGER[3], H. UNSAL[2], H. M. KAMENS[4], T. AREFIN[2];
[2]Neurosci., [1]Univ. of Rochester Med. Ctr., Rochester, NY; [3]Biomed. Engin., Pennsylvania State Univ., University Park, PA; [4]Biobehavioral Hlth., Penn State Univ., University Park, PA

Abstract: Alcohol use disorder (AUD) affects over 28 million people in the US, however, only 7% of those with past year AUD received treatment, deeming it as the most undertreated substance use disorder. At the neurobiological level, alcohol acts as a complex agent that alters multiple molecular pathways, including those involving glial cells—and leads to changes in brain structure and function, particularly in regions critical for executive functions (EF). Though evidence suggests females may be more susceptible to EF deficits, the impact of sex-based differences remains understudied. Therefore, we aim to bridge the gap by integrating high-resolution multiparametric diffusion MRI (dMRI) with light sheet microscopy (LSM) to decipher the most comprehensive microstructural fingerprints from circuits to the cellular level using a mouse model of chronic intermittent ethanol exposure. Male and female C57BL/6J (n=40, P60) mice were chronically exposed to alcohol for 7 weeks using the every-other-day (EOD) paradigm, followed by ex vivo dMRI and LSM. Voxel-based analysis of the dMRI data demonstrated brain-wide changes in volume, axial diffusivity, and fractional anisotropy due to alcohol. Significant changes were identified in 30 brain regions instrumental for EF including prefrontal cortex (PFC), hippocampus (HIP), basal ganglia, thalamus, and amygdala. Five major networks exhibited significant alterations in structural connections following alcohol use. Most

structural connections were significantly reduced within the cortico-hippocampal network in alcohol-exposed female mice. Furthermore, the HIP and PFC of alcohol exposed mice had a significant decrease in degree centrality and nodal efficiency. A pipeline for subject-specific co-registration of the dMRI data with each 3D LSM image to spatially align regions of interest within the same samples was developed. Using MuVI-SPIM 10x objective), we imaged the HIP for myelin basic protein (MBP) and ionized calcium-binding adapter molecule 1 (IBA1) to link circuit-level dynamics with cellular responses. Our preliminary data indicate a trend toward increased IBA1+ expression, ramification, and volume, as well as altered MBP+ expression in alcohol-exposed mice. Overall, utilizing a multimodal imaging approach, we demonstrated a significant reduction in axonal connections at the circuit level, while also identifying a trend toward increased local neuroinflammation in the HIP of alcohol-exposed mice. Our study provides mechanistic insight into how chronic alcohol use influences neuroinflammation and neurodegeneration in the hippocampal-associated networks that disturbs EF in a sex-specific manner.

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Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

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Time: Sunday, November 15, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO14.06

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA026820

Title: Activation of the orphan receptor GPR88 reduces morphine reward and neuron-driven reinforcement

Authors: C. JIN[1], M. RAHMAN[2], ***E. DARCQ**[3];
[1]RTI Intl., Apex, NC; [2]RTI Intl., RTP, NC, ; [3]INSERM, Strasbourg, France

Abstract: The orphan G protein-coupled receptor GPR88 is highly enriched in striatal circuits and has emerged as a promising target for neuropsychiatric disorders, including substance use disorders. Previous genetic studies suggest that GPR88 modulates responses to drugs of abuse, but the behavioral consequences of pharmacological GPR88 activation in opioid-related behaviors remain poorly understood. Here, we evaluated the effects of the brain-penetrant GPR88 agonist RTI-122 on morphine-induced behavioral responses and mu opioid receptor (MOR) neuron-dependent reinforcement in mice. First, RTI-122 transiently reduced spontaneous locomotor activity during the first 30 min after injection in wild-type mice, an effect absent in Gpr88 knockout mice, supporting GPR88-specific action. RTI-122 also dose-dependently reduced morphine-induced hyperlocomotion, with significant effects during the first 60 min

following morphine administration. We next assessed morphine reward using conditioned place preference (CPP). Morphine induced a robust place preference, whereas co-administration of RTI-122 significantly reduced morphine CPP. RTI-122 alone did not induce place preference or aversion, indicating that GPR88 activation reduces morphine reward without producing intrinsic motivational effects. To test whether RTI-122 affects reinforcement driven by opioid-defined circuits, we developed an opto-intracranial self-stimulation paradigm in MOR-Cre mice expressing the inhibitory opsin GtACR2 in VTA MOR neurons. Mice self-administered optogenetic inhibition of VTA MOR neurons, consistent with a reinforcing disinhibition of mesolimbic dopamine signaling. RTI-122, administered 1 h before testing to avoid locomotor confounds, significantly reduced active but not inactive nosepokes. Finally, RTI-122 did not alter elevated plus maze behavior, suggesting no anxiogenic-like effects. Together, these findings identify GPR88 activation as a promising strategy to reduce morphine reward and MOR circuit-mediated addiction-like behaviors.

Disclosures: C. Jin: None. **E. Darcq:** None.

Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

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Presentation Number: NANO14.07

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA056660
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R01DA045836

Title: Neuroadaptations in Opioid Responsive Prefrontal Ensembles by a Psychedelic-like Therapeutic

Authors: *J. PETERS;
U. of Alabama at Birmingham, Birmingham, AL

Abstract: Tabernanthalog is an ibogaine-analog devoid of the hallucinogenic and cardiotoxic properties of its parent compound. It acutely elevates serotonin, norepinephrine, and to a lesser extent dopamine, in the prefrontal cortex, and produces both acute and lasting reductions in heroin seeking after a single dose. Using in vivo fiber photometry, we identified two distinct neuronal ensembles in the prefrontal cortex with increased calcium transients in response to heroin-paired cues. These ensembles were defined by their distinct projections to the lateral hypothalamus versus the nucleus accumbens shell. Despite similar heroin-cue reactivity, these ensembles were found to serve opposing functional roles in heroin seeking using an optogenetic strategy to manipulate their cue reactivity. This study aimed to identify whether tabernanthalog

induces transcriptomic changes in each of these neuronal ensembles. To do this, we performed single nucleus RNA sequencing (snRNA-seq) from the prefrontal cortex of rats that underwent heroin self-administration (versus saline controls) and acute treatment with tabernanthalog (or saline vehicle) prior to tissue collection. Results indicate cell-type specific regulation of the prefrontal cortex transcriptome, not only by heroin, but by tabernanthalog therapy as well. By combining snRNA-seq with viral projection mapping, we identified which of these cell-types project to the lateral hypothalamus versus the nucleus accumbens shell. This study reveals not only the molecular encoding of opioid pathology in the prefrontal cortex, but its reversal by a synthetic, clinically promising non-hallucinogenic psychedelic-inspired therapeutic.

Disclosures: J. Peters: None.

Nanosymposium

NANO14: Neural Circuits of Alcohol and Drug Use: From Consumption and Craving to Compulsion and Treatment

Location: WCC Rm 146C

Time: Sunday, November 15, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO14.08

Topic: H.08. Drugs of Abuse and Addiction

Title: Focal transcranial magnetic stimulation (TMS) of rat mPFC prevents incubation of cocaine craving and restores functional connectivity

Authors: *H. LU[1], S. HOFFMAN[2], Z. MA[3], A. CARNEY[4], T. SCOTT[1], Z. XI[5], Y. SHAHAM[6], Y. YANG[7];
[1]Natl. Inst. on Drug Abuse, NIH, Baltimore, MD; [2]NIH, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [3]NIH, NIDA IRP, Baltimore, MD; [4]NIH, Frederick, MD; [5]Intramural Res. Program, Natl. Inst. on Drug Abuse, Baltimore, MD; [6]Behavioral Neurosci. Br., IRP/NIDA/NIH, Baltimore, MD; [7]Natl. Inst. of Drug Abuse, Baltimore, MD

Abstract: Background: Relapse remains a central obstacle in the treatment of cocaine use disorder (CUD), for which no medications have received approval from the U.S. Food and Drug Administration. Transcranial magnetic stimulation (TMS) has shown promise as a potential therapeutic intervention. However, current clinical trials often rely on a “trial-and-error” approach in target selection and experimental design. We previously developed a novel TMS platform and high-density theta burst stimulation (hdTBS) technology, enabling precise, focal stimulation of the rat medial prefrontal cortex (mPFC), including the prelimbic and anterior cingulate cortices.**Methods:** We applied hdTBS intervention to a well-established rat model of cocaine relapse and craving after cessation of extended access intravenous drug self-administration and assessed brain response using resting-state functional magnetic resonance imaging (fMRI).**Results:** As expected, we observed robust time-dependent increases in cocaine seeking (incubation of cocaine craving) in control rats receiving sham stimulation over 3 weeks of abstinence accompanied by a reduction in prefrontal functional connectivity. In contrast, daily sessions of hdTBS for 7 days delivered on abstinence days 14-20 prevented the emergence of the

incubation effect and restored prefrontal network functional connectivity.**Conclusions:** This study provides strong preclinical evidence demonstrating that precise circuit modulation of medial prefrontal subregions causally reverses both behavioral and network-level adaptations associated with relapse vulnerability. Given the clinical accessibility and established safety profile of TMS, this work provides a mechanistically grounded framework for target selection and supports the translation of focal TMS of the mPFC for relapse prevention in CUD patient.

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Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.01

Topic: I.10. Human Learning and Cognition

Title: Attentional mechanisms in blocked category learning: Verbal evidence from rule predictions

Authors: *J. J. CONTI, K. R. KOEDINGER, P. F. CARVALHO;
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Blocked presentation of information is thought to provide benefits over interleaving by directing attention to commonalities. However, most current evidence is indirect, in the form of posttest performance and eyetracking. In this study, participants learned to classify bugs organized around a relational rule in a 2x2 design manipulating blocked vs. interleaved presentation and example presence vs. absence. Throughout the task, we ask participants to make predictions about the organizing rule.
Blocked presentation promoted better post-test performance and more relational feature verbalizations than interleaved; removing examples amplified feature use in both conditions. Moreover, greater increases in relational verbalizations during training positively predicted posttest performance, particularly for blocked learners, suggesting presentation format shapes reasoning trajectories.

Disclosures: J.J. Conti: A. Employment/Salary (full or part-time):; Carnegie Mellon University. **K.R. Koedinger:** A. Employment/Salary (full or part-time):; Carnegie Mellon University. **P.F. Carvalho:** A. Employment/Salary (full or part-time):; Carnegie Mellon University.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.02

Topic: I.10. Human Learning and Cognition

Title: Blocking, interleaving, and scaffolding in acquired equivalence

Authors: *K. BRANNIGAN, T. HOUSER, L. COSTA, D. ZEITHAMOVA;
Psychology, Univ. of Oregon, Eugene, OR

Abstract: We use memory to both remember prior experiences and to generalize beyond them. In acquired equivalence, learners show generalization of knowledge across related stimuli, but whether this generalization reflects an integrated schema formed during encoding or retrieval-based inference across separately learned associations is debated. Here, we hypothesized that the formation of knowledge and its generalization may depend on how related learning experiences are sequenced. We tested how blocking, interleaving, and a scaffolded combination of the two influence learning and generalization in an acquired equivalence paradigm. The scaffolded condition began with blocked training, allowing participants to establish one set of associations before related information was introduced, and then shifted to interleaving to encourage comparison across trial types. Final test included both learned relationships and generalization. We found fastest learning in the blocked condition, but this advantage did not transfer to the test. We found no evidence for memory integration after neither blocking nor interleaving, but the scaffolded combination of the two yielded the strongest final test performance and generalization. This pattern suggests that order of experience matters: early blocked learning may support stable acquisition of associations, whereas later interleaving may promote flexible use of information abstracted across experiences. Nevertheless, the observed generalization pattern was more consistent with retrieval-based inference than with integration during encoding, suggesting that learners responded to generalization probes by recombining separate associations on-demand at test. These findings identify scaffolding as a useful training procedure for acquired equivalence and clarify how sequencing experience shapes learning and generalization.

Disclosures: K. Brannigan: None. **T. Houser:** None. **L. Costa:** None. **D. Zeithamova:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.03

Topic: I.10. Human Learning and Cognition

Support: NIH Grant R01 MH129436

Title: Curriculum Effects in Associative Inference: How Interleaving Episodes Promotes Integrated Representations and Blurs Memory

Authors: *A. GORDIENKO, A. C. SCHAPIRO;
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Abstract: Memory theorists have debated to what extent and under what conditions memories of distinct experiences become integrated. Further, when integration does occur, theories differ as to whether this integration comes at the expense of fidelity of the memories for the individual experiences. Prior work has found that interleaved learning of object pairs (AB and BC) leads to integrated representations of distinct items (A and C) akin to those of a canonical neural network model employing distributed representations and exposed to information in interleaved order. We have proposed in the C-HORSE model of the hippocampus that this kind of integration may be happening along the monosynaptic pathway, in contrast to the trisynaptic pathway which maintains pattern separated representations that are curriculum agnostic. Such models would also predict a lower fidelity representation of the constituent individual memories relative to a model specialized for episodic encoding. Here we sought to replicate the prior findings and test whether constituent memories do show this blurring under conditions in which episodic retrieval is unlikely, using a paradigm where memory for perceptual details of the direct memories can be easily assessed. In a behavioral experiment, 34 participants learned chains of associate pairs composed of novel objects that shared overlapping items but with altered visual features. Specifically, participants learned that object A was related to B and that B' was related to C, where B and B' were the same object but viewed from a different angle. Eight pairs were learned in an interleaved curriculum and eight in a blocked curriculum. Memory for direct pairs (AB), adjacent pairs (AB'), and indirect pairs (AC) was then tested in a speeded recognition task and two non-speeded explicit inference tasks. We found that interleaved learning led to integrated representations of indirect associates (AC), replicating existing findings. Furthermore, we found that increased false alarms for unseen but perceptually similar associates (AB') in the interleaved condition suggested generalized memory for associated objects, providing additional support that interleaving promotes integration. These behavioral findings are consistent with accounts of memory integration based on interleaved learning in neural network models employing distributed representations. Forthcoming fMRI work aims to illuminate the neural underpinnings of these curriculum effects and characterize the nature of these integrated representations both immediately following learning and after a one-week delay.

Disclosures: A. Gordienko: None. **A.C. Schapiro:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.04

Topic: I.10. Human Learning and Cognition

Support: NSF DGE-1839285
NIH R21AG072673

NIH R01AG088306
NIH F32AG072836

Title: The order of experience shapes multi-step representations through multi-step decisions across multiple species

Authors: *K. W. COOPER[1], S. M. NOH[3], C. E. STARK[1], N. J. FORTIN[4], A. BORNSTEIN[2]; [1]Neurobio. and Behavior, [2]Cognitive Sci., Univ. of California, Irvine, Irvine, CA; [3]Cognitive Sci., Univ. of California Irvine, Irvine, CA; [4]Dept. of Neurobio. and Behavior, UC Irvine, Irvine, CA

Abstract: Effective goal-directed decision making relies on memory and planning, processes that depend on the hippocampus to determine how experiences are ordered and integrated into internal representations. Foundational work spanning species suggests that such representations are shaped by constraints on encoding abilities and by the prevalence and extent of subsequent reactivation. To examine the structure of state representations, we developed tasks for both humans and rodents that measure the ability to learn and make multi-step inference judgments about associations among sequences of interconnected stimuli. When examining the relationship between inference judgments and encoding ability in humans, we observed that successful latent learning and inference can occur reliably, and judgment performance was explained by individual mnemonic discrimination ability. We further examined how the structure of experience affects inference judgments by utilizing "blocked" versus "intermixed" training sequences. While an intermixed schedule benefited individuals with high mnemonic discrimination, a blocked schedule selectively improved performance for those with low mnemonic discrimination. We propose that the mechanisms underlying this difference span encoding and consolidation processes. First, by training connectionist models on the same multi-step inference task as humans, we show that the effect of "blocked" versus "interleaved" stimulus presentations can be reproduced by manipulating the memory capacity of the network. Second, by recording hippocampal activity while rats remembered an extended sequence of nonspatial events, we show that hippocampal replay extends to multi-step sequences. Leveraging a rigorous statistical framework for quantifying sequences of discontiguous states, we discovered forward and reverse replay of the sequential relationships across events. Such replay events can occur during awake periods, can occur between events, and, critically, are sensitive to order-memory judgments. These findings suggest that the order effects that shape neural representations are driven by both initial encoding demands and subsequent offline reactivation, towards guiding the development of approaches to preserve decision-making abilities through memory-based training interventions.

Disclosures: K.W. Cooper: None. **S.M. Noh:** None. **C.E. Stark:** None. **N.J. Fortin:** None. **A. Bornstein:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.05

Topic: I.10. Human Learning and Cognition

Support: LRSF Fellowship/Simons Foundation
DP2 MH129958-01
IOS-2145814

Title: Structured experience shapes strategy learning and neural dynamics in the medial entorhinal cortex

Authors: *J. C. BOWLER[1], D. B. AZHAR[1], C. M. JENSEN[2], H.-W. LEE[3], J. G. HEYS[2]; [2]Neurobio., [3]Dept. of Neurobio., [1]Univ. of Utah, Salt Lake City, UT

Abstract: Animals can solve new, complex tasks by reusing and adapting what they have learned before (Elio & Anderson, 1984). This kind of flexibility depends not just on having prior experience, but on how that experience was structured in the first place. The design of early training curriculum is especially important: poorly structured experiences can hinder abstraction and limit generalization, while carefully structured training promotes more flexible and adaptive behavior. Yet, the neural mechanisms through which experience influences future learning remain unclear. To investigate how early training shapes learning we first trained recurrent neural networks (RNNs) on variants of an odor-timing task previously used to study complex timing behavior in mice (Bigus et al. 2024). We then tested the RNN predictions on the effect of previous experience on generalization in mice trained on the same task using staged training sequences. Using behavioral and electrophysiological recordings in the medial entorhinal cortex—a recurrently organized region implicated in context-dependent and timing-related dynamics--we find remarkable similarity with the model predictions. Both RNNs and mice trained without well-structured early experience developed rigid strategies and made repeated errors. In contrast, those given more balanced early training were better able to generalize and showed similar neural activity patterns that reflected the task's underlying temporal structure. Using dynamical systems approaches (Vyas et al. 2020), we reveal a mechanism for this effect: networks trained with appropriately structured curricula developed distinct dynamical motifs that support the correct abstractions when complexity was increased. Networks that lacked early training or received remedial curricula developed single fixed-point solutions that failed to generalize beyond the training stimuli. Together, these findings demonstrate that it is not just the presence of prior experience, but also its structure, that governs how flexible and generalizable knowledge emerges in both biological systems and computational models.

Disclosures: J.C. Bowler: None. **D.B. Azhar:** None. **C.M. Jensen:** None. **H. Lee:** None. **J.G. Heys:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.06

Topic: I.10. Human Learning and Cognition

Support: R01AG088306
R01NS119468

Title: Memory-regularized variational autoencoders capture training sequence effects and develop predictive sparse representations connecting to a successor representation

Authors: *S. GUO[1], D. ZHOU[2], X. R. CHEN[3], A. BORNSTEIN[3];
[1]Univ. of california, Irvine, Irvine, CA; [2]university of california, irvine, Long Beach, CA; [3]Univ. of California, Irvine, Irvine, CA

Abstract: Cognitive maps are thought to carry information about both directly observed associations and also longer predictive paths through an environment. Recent work further suggests that human hippocampal and entorhinal neurons encode the temporal structure of experience in a manner qualitatively consistent with a predictive ("successor") representation, yet the factors that influence how such diverse representations emerge from memory encoding circuits remain unclear. Here, we connect neural network simulations of memory-guided inference with a memory-regularized variational autoencoder (VAE) framework to test how learning sequence, memory capacity, and representational sparsity shape latent associative structure. Building on prior work showing that blocked and interleaved learning schedules can produce opposing effects on integration versus separation, we show that these discrepancies can be explained by interactions between memory constraints and coding style: blocked learning promotes integration when memory capacity is low, whereas interleaved learning promotes integration when memory capacity is high. Across simulations, sparse codes tended to protect distinct direct associations, while sparse-but-distributed latent codes were especially likely to support integrated, map-like representations. We then asked whether a memory-regularized VAE could form latent representations resembling a successor representation. By combining reconstruction with a memory-similarity regularization objective, the model learned representations that preserved direct associations while also capturing graded predictive relationships among indirectly connected stimuli. These results suggest that successor-like structure can arise from the same computational pressures that shape sparse associative maps: compression, capacity limits, and the need to preserve behaviorally relevant relational information across overlapping experiences. Together, this framework links episodic integration and separation with predictive coding in hippocampal-entorhinal systems, providing a mechanistic account of how learning sequence and memory constraints shape sparse associative representations that support inference, generalization, and planning.

Disclosures: S. Guo: None. **D. Zhou:** None. **X.R. Chen:** None. **A. Bornstein:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

Location: WCC Rm 145

Time: Sunday, November 15, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO15.07

Topic: I.10. Human Learning and Cognition

Support: COBRE CNSF Pilot Award (1P20 GM103645)

Title: Dynamic noise correlations between feature-selective brain regions support efficient learning

Authors: *J. KIM[1], X. C. DAI[2], A. BHANDARI[3], M. R. NASSAR[4];
[1]Brown Univ. Neurosci. Grad. Program, Providence, RI; [2]Neurosci., [3]Cognitive Linguistics and Psychological Sci., [4]Metcalf Hall, Brown Univ., Providence, RI

Abstract: Learning to assign credit to relevant features is a challenging problem. Recent theoretical work has demonstrated that stimulus-independent covariation in trial-to-trial neural activity fluctuations may reflect a dimensionality reduction mechanism that facilitates faster and more robust learning, but this proposal has yet to be empirically verified. Here we performed an empirical test of this theory by combining computational modeling, functional magnetic resonance imaging, and behavioral measures. Forty-seven human subjects performed a task requiring discrimination of multi-dimensional perceptual stimuli while undergoing fMRI. In each block of trials, subjects learned a classification boundary in a two-dimensional feature space (color and motion) that was translated occasionally and unpredictably, forcing them to learn continuously on one of two possible joint feature dimensions (color+motion or color-motion, depending on block). A two-layer feedforward neural network performing this task showed that amplifying gain along task-relevant dimensions produced noise correlations aligned to these dimensions and enhanced learning. Human behavioral data was best fit by models with higher gain on task-relevant dimensions, suggesting that subjects focused on and updated the joint-feature dimensions that were most important for learning and task performance, and raising the question as to whether humans would show dynamic modulations of noise correlations across blocks to shift learning onto the relevant task dimension akin to gain adjustments in the model. Concurrently collected fMRI data revealed that noise correlations across feature-sensitive regions are modulated in a task-dependent manner, in line with this basic model prediction. Specifically, when residual fMRI data were passed through decoders trained on color and motion respectively, noise correlations between the resulting feature noise vectors were more positive during [color+motion] learning blocks and more negative during [color-motion] learning blocks, supporting the idea that the brain dynamically amplifies task-relevant dimensions to improve learning.

Disclosures: J. Kim: None. **X.C. Dai:** None. **A. Bhandari:** None. **M.R. Nassar:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

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Topic: I.10. Human Learning and Cognition

Support: NIH R03MH128628
NIH R01DA055259
NIH R01HD098097
NIH R01HD099165
NIH R21HD098509

Title: Repeated study facilitates differentiation of hippocampal neural representations

Authors: *E. T. COWAN[1], B. TANRIVERDI[2], I. R. OLSON[3], J. M. CHEIN[4], V. P. MURTY[5]; [1]Adelphi Univ., Garden City, NY; [2]Biostatistics, Epidemiology and Informatics, Univ. of Pennsylvania, Philadelphia, PA; [3]Psychology & Neurosci., [4]Psychology, Temple Univ., Philadelphia, PA; [5]Psychology, Univ. of Oregon, Eugene, OR

Abstract: The hippocampus has long been a focus of neuroscience research for its importance in processing newly learned information. However, little is known about how hippocampal representations evolve with repeated study of the same information. Here, we used a combination of fMRI-based analyses and theoretically-inspired computational modeling to track how patterns of hippocampal representations evolve across repetitions. While in the scanner, participants viewed image-location pairs that were repeated four times. Using representational similarity analysis, we found pattern similarity for each pair decreased across consecutive repetitions in the hippocampus, but did not change in cortical regions. To elucidate the mechanisms underlying such changes, we generated seven theoretical models simulating distinct voxel-level dynamics. The best fitting model reflected a hybrid process, combining updating of representations across repetitions, consistent with new learning, and pruning of otherwise stable voxels. These findings demonstrate that repetition drives differentiation in hippocampal representations, arising from a balance between incorporating new information and preserving prior representations.

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Nanosymposium

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Topic: I.10. Human Learning and Cognition

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F31NS105353 to S.M.N.
F32AG072836 to S.M.N.
R01MH100121 to A.R.P
F32MH114869 to N.W.M.

Title: Interleaved learning shapes neural representations in medial prefrontal cortex to enhance real-world category knowledge

Authors: *S. M. NOH[1], N. W. MORTON[2], A. M. BORNSTEIN[1], A. R. PRESTON[3]; [1]Cognitive Sci., Univ. of California Irvine, Irvine, CA; [2]Dept. of Psychology, Univ. of Wisconsin–Milwaukee, Milwaukee, WI; [3]Neurosci., The Univ. of Texas at Austin, Austin, TX

Abstract: Real-world reasoning often depends on generalizing knowledge from prior experience to novel situations. For instance, one can identify the genre of a new album by comparing it to previously encountered music. Prior neuroscientific work has implicated the hippocampus and medial prefrontal cortex (mPFC) in category learning, particularly when learners must attend to feature dimensions that define category membership. However, learning naturalistic categories may rely less on identifying a small set of easily separable dimensions and more on differentiating exemplars from competing categories. Unlike work on artificial or rule-based category learning, relatively little is known about the factors that shape neural differentiation of natural category representations or how such differentiation supports generalization to novel exemplars. Extensive behavioral work has identified that one factor that may critically influence category representations is learning schedule: interleaved presentation of exemplars from different categories may promote discriminative contrast between categories, relative to blocked presentation. We used fMRI to test how learning schedules shape neural representations for naturalistic painting categories. Participants learned to classify paintings by 6 different artists under blocked and interleaved presentation schedules. Item-level neural representations were measured before and after learning to examine how similarity among same- and different-category exemplars changed as a function of study schedule. Interleaved learning led to greater category discriminability in the hippocampus and dorsal mPFC relative to blocked learning. Moreover, participants who showed greater interleaving-related category discriminability in dorsal mPFC also showed a larger behavioral benefit of interleaving when classifying novel exemplars. These findings suggest that juxtaposing exemplars from different categories can highlight category-diagnostic distinctions, leading to more discriminable neural representations that support generalization to new real-world categories. More broadly, this work shows that the order of learning experiences can shape neural representational structure in ways that directly relate to flexible category generalization.

Disclosures: S.M. Noh: None. **N.W. Morton:** None. **A.M. Bornstein:** None. **A.R. Preston:** None.

Nanosymposium

NANO15: Behavioral and Neural Insights Into Representational Learning

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Presentation Number: NANO15.10

Topic: I.10. Human Learning and Cognition

Support: Wellcome Trust Discovery Award 227928/Z/23/Z
Wellcome Trust Henry Dale Fellowship 223263/Z/21/Z
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Title: Neural Geometry Supporting Compositional Generalization

Authors: *Z. LIANG[1], L. GLITZ[2], M. C. KLEIN-FLÜGGE[3], C. SUMMERFIELD[4];
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Abstract: Compositionality is a remarkable feature of human cognition. Humans have the capacity to break down learned knowledge into constituents and later reassemble (infinite) novel combinations from the limited set of known individual constituents. Here, we examine this ability with a paradigm in which participants have to make novel inferences by combining the meaning of symbolic features. In this task, two sets of symbolic features (colour and animal shape) indicate spatial positions on the two Cartesian axes. We generated 25 stimuli from the factorial combinations of five colours and five animal shapes. Participants associatively learned the locations of 9 stimuli with feedback and were tested on the remaining 16 untrained colour-animal combinations without feedback. Therefore, to solve the task, participants would have to break down the training stimuli into colour and shape rules and then compose the locations for the novel stimuli based on the rules. Prior work demonstrated that human generalisation benefits from a training regime in which items are axis-aligned and temporally correlated. The current work leveraged fMRI to investigate the neural geometry supporting compositional generalisation in participants who were trained using this curriculum and generalised successfully (N=41). Using a variety of multivariate analyses, we found distinct representation geometry across our regions of interest. The hippocampus encoded the symbolic features in a high-dimensional, parallel format that permitted flexible individuation. In ventromedial prefrontal cortex (vmPFC), posterior parietal cortex (PPC) and primary visual cortex (V1), neural patterns for novel stimuli (composites) could be predicted as a linear combination of signals for training stimuli (elemental symbolic features). In vmPFC, this composition occurred in a high-dimensional format. But in PPC and V1, it took place in a low-dimensional format, which resulted in a representation that reconstructed the 2D map of the corresponding locations for the test stimuli. Together, these results suggested that rule information was represented in the hippocampus and was composed to solve the generalisation problem by the vmPFC in a high-dimensional space. The PPC potentially acted as a readout region that transformed the stimuli into a spatial frame of reference for motor output.

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Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.01

Topic: A.06. Developmental Disorders

Support: NIH R01 NS114253

Title: Muscleblind-like RNA binding protein localizes mRNAs in neurons through molecular interactions with early endosomes

Authors: *A. JANUSZ-KAMINSKA[1], E. KHAN[1], A. SHEN[1], P. FERNANDEZ[2], L. A. KNUDSON[1], R. HILDEBRANDT[2], E. ZHOU[1], E. T. WANG[2], G. J. BASSELL[1];
[1]Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA; [2]Mol. Genet. and Microbiology, Univ. of Florida, Gainesville, FL

Abstract: Transport of mRNAs and localized translation are crucial for neurodevelopment and function. Recent findings revealed a role of endosomes in RNA transport and localized translation in conjunction with RNA binding proteins (RBPs). Muscleblind-like (MBNL) proteins are RBPs that regulate splicing and mRNA localization. MBNLs are depleted from the cytoplasm in myotonic dystrophy type 1 (DM1) by sequestration on the expanded CTG repeats in the 3' UTR of dystrophia myotonica protein kinase (DMPK) transcripts. We have shown a role for MBNL-kinesin interactions in mRNA localization although the role of membrane association is not well understood. Colocalization of MBNL1 with early (Rab5), late (Rab7) and recycling (Rab11) endosomes was observed in n2a cells. EGFP-MBNL1 co-transport with endosomes and lysosomes (Rab5, Rab11, Rab7, Lamp1) in neuronal processes was observed. Expression of EGFP-MBNL1-41, but not a C-terminus deletion mutant of MBNL1, decreased movement of Rab5 and Rab11 endosomes. Overexpression of mCherry-Rab5, but not its dominant negative (S43N) mutant decreased EGFP-MBNL1 motility. STED live imaging with MCP-Halo artificial reporter system revealed that MBNL1-mRNA distribution was dependent on Rab5 early endosomes. Pulldown experiments showed that the association of MBNL1 with Rab5 endosomes is dependent on both C-terminal domain and RNA binding. Lastly, distribution of endogenous *Snap25* mRNA was dependent on MBNL1 C-terminus. Work in progress is to evaluate role of MBNL1 C-terminus in local translation of SNAP25. We conclude that MBNL1 mRNA granules are transported with early, recycling and late endosomes and that the C-terminus of MBNL1 acts as an anchor that drives RNA granule formation and bi-directionally regulates its mobility with endosomes. We propose that endomembrane anchoring is crucial for distal localization of MBNL1 target mRNA in neurons. This work was supported by an NIH R01 NS114253 awarded to G.J.B and E.T.W.

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Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

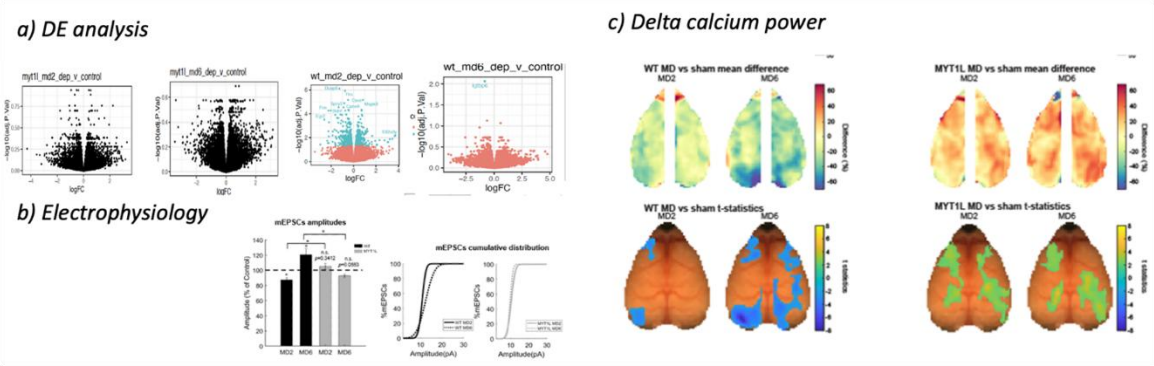
Presentation Number: NANO16.02

Topic: A.06. Developmental Disorders

Title: MYT1L haploinsufficiency impairs critical period experience-dependent plasticity

Authors: *M. ABIJAOUDE[1], J. D. DOUGHERTY[4], J. P. CULVER[2], R. CHASE[5], K. B. HENGEN[6], S. CHEN[7], R. RAHN[8], J. PADAWER-CURRY[9], L. TIAN[10], M. E. LAMBO[3], A. BICE[3];
[1]Washington Univ. in St Louis, st louis, MO; [2]Radiology, Washington Univ. in St Louis, Webster Groves, MO; [3]Washington Univ. in St Louis, St Louis, MO; [4]Washington Univ. Sch. of Med., St. Louis, MO; [5]Washington Univ. Sch. of Med. in St. Louis, Saint Louis, MO; [6]Biol., Washington Univ. In St. Louis, Saint Louis, MO; [7]Radiology, Washington Univ. in St. Louis, Stuart, FL; [8]Weill Cornell Med., New York, NY; [9]Optical Radiology, Washington Univ. at St. Louis, St. Louis, MO; [10]Univ. of Washington, Seattle, WA

Abstract: Monocular deprivation (MD) is a classic paradigm to induce experience-dependent plasticity in rodents. In humans, MYT1L deficits cause neurodevelopmental diagnoses (NDDs), such as Intellectual Disability and autism. MYT1L syndrome is caused by heterozygous loss-of-function mutations in the proneural transcription factor MYT1L. Patients with the loss-of-function mutation in MYT1L exhibit many types of developmental anomalies. Using critical period monocular deprivation as a model to drive experience-dependent plasticity, we first established WT mice's responses to MD across three scales of investigation: gene expression and excitatory postsynaptic adaptations in the visual cortex and network-level resting-state functional connectivity (rsFC) in the cortex. The highly stereotyped trajectory of the response to MD in the visual system makes it a good model to evaluate the roles of genetic mutations on experience-dependent plasticity.In gene expression, we found that MD downregulates visual cortex IEG expression in both WT and MYT1L-het mice. In physiological studies, we found that prolonged MD in WT mice caused a biphasic change in excitatory postsynaptic strength. Opposite to WT mice, mean visual cortex mEPSC amplitudes in MYT1L-het mice failed to undergo a reduction following MD2 (two days post MD) and trended toward a *reduction* at 6d MD. Beyond the visual cortex, we measured rsFC using wide-field fluorescence optical imaging (WFOI) and found that MYT1L mutation disrupts the network properties associated with experience-based plasticity that are seen in the WT MD mice when comparing delta calcium power and resting state functional connectivity. We found that, across all scales the response of MYT1L mice was substantially disrupted, indicating that the system cannot adapt.



a) Differentially Expressed Gene analysis. While we saw no significant differences in gene expression in the MYT1L deprived versus control hemispheres at either time point, we did observe robust differences in the WT mice, especially at MD2. For the MYT1L Hets, we observed no significant DEGs and no genotype-by-deprivation interaction in a two-factor model. b) Electrophysiology. V1 mEPCS amplitudes underwent a significant reduction after MD2 but a significant increase after MD6 for WT, whereas in MYT1l the mEPCS amplitudes failed to reduce after MD2 and continued to increase by MD6. At MD6, the distribution shifted to the right relative to MD2. Whereas there is no significant change in the distribution of mEPSC amplitudes at MD2 and MD6 for MYT1L MD. c) Delta Calcium Power. For WT mice compared to sham, a statistically significant reduction of delta calcium power in the deprived visual cortex at MD2 and MD6 —confirming an expected reduction in spontaneous neural activity as a result of MD. Whereas for MYT1L MD mice compared to sham, saw no significant statistical change in visual cortex and little statistical change.

Disclosures: M. Abijaoude: None. **J.D. Dougherty:** None. **J.P. Culver:** None. **R. Chase:** None. **K.B. Hengen:** None. **S. Chen:** None. **R. Rahn:** None. **J. padawer-curry:** None. **L. Tian:** None. **M.E. Lambo:** None. **A. Bice:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.03

Topic: A.06. Developmental Disorders

Title: Developmental and genetic vulnerability to sleep loss converge on excitatory/inhibitory synaptic maturation

Authors: *E. CHARTAMPILA, J. S. LORD, G. H. DIERING;
Cell Biol. and Physiol., Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Sleep dynamically regulates neuronal synapses, but its role may be especially consequential during development, when neural circuits undergo extensive structural remodeling as synapses are formed, eliminated, and stabilized. This is particularly relevant to autism spectrum disorder (ASD), where synaptic dysfunction is a core biological feature, and sleep disruption commonly emerges early in life and is associated with adverse developmental outcomes. However, it remains unclear how the developing brain is uniquely impacted by sleep

disruption and how developmental vulnerabilities interact with ASD genetic risk. To identify developmental vulnerabilities to sleep loss, we compared behavioral and synaptic responses to acute sleep deprivation (SD) in juvenile (~P21) and adult (~P70) mice. Compared to adults, juveniles exhibited blunted sleep recovery following SD, precipitating cognitive impairment. SD in juveniles, but not adults, drove a significant increase in excitatory and inhibitory synapse density in the hippocampus and cortex, suggesting that sleep actively supports synapse maturation and the establishment of excitatory/inhibitory (E/I) balance. Next, we examined the interaction between developmental SD and ASD genetic risk using juvenile Shank3ΔC+/- (HET) mice. Compared to wild-type littermates, HET mice responded to SD with an exaggerated excitatory synaptogenesis response, whereas SD-induced inhibitory synaptogenesis was absent. These findings indicate that Shank3 haploinsufficiency shifts the developmental response to SD, compounding E/I imbalance in the context of underlying ASD genetic risk. This study defines development as a period of unique vulnerability to sleep loss and identifies synapse maturation as a point of convergence between the negative impacts of sleep disruption and ASD genetic risk.

Disclosures: E. Chartampila: None. **J.S. Lord:** None. **G.H. Diering:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

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Presentation Number: NANO16.04

Topic: A.06. Developmental Disorders

Support: SFARI #970806

Title: Sleep experience, genetic vulnerability, and biological sex determine synaptic ontogeny through synaptic translational regulation.

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Abstract: Sleep disruption is highly prevalent in autism spectrum disorder (ASD), however whether sleep disruption is a symptom or causal driver of ASD etiology is not clear. Our previous work established that a heterozygous deletion of the 22nd exon Shank3$^{(+/-)22ex}$ enhanced vulnerability to early-life sleep disruption (ELSD), resulting in lifelong sex specific behavioral deficits. Using proteomics discovery, we identify synapse maturation as a unique vulnerability to developmental sleep loss. Together, these findings suggest that developmental sleep disruption interacts with genetic vulnerability to causally shapes long lasting behavioral deficits and brain function. However, the alterations in synaptic proteome in consequence to ELSD remain unknown. To address this knowledge gap, we defined the impact of ELSD treatment in wild-type

and Shank3$^{(+/-)22ex}$ ASD model littermates using synapse fractionation and proteomics. We first demonstrate that heterozygous and homozygous Shank3 mutation produced brain region- and sex- specific remodeling of the synaptic proteome, revealing gene and sex interaction. We then isolated synapse fractions from cortex, hippocampus and striatum from WT and Shank3$^{(+/-)22ex}$ animals subjected to ELSD, or control treatment. We observed brain region and sex specific effects of ELSD in both WT and Shank3$^{(+/-)22ex}$. Gene ontology identified synaptic protein translation and translation associated ontologies as key ELSD disrupted processes in male and female Shank3$^{(+/-)22ex}$ mice. Dysregulated protein translation is implied in ASD, here we observe that ELSD results in alteration in proteins that regulate translation in Shank3$^{(+/-)22ex}$ mice. These findings establish synaptic translation as a central mechanism through which genotype, sex and developmental sleep disruption interact to shape synaptic ontogeny.

Disclosures: J. Anantha: None. **J.S. Lord:** None. **K.K. Joyce:** None. **S. Grizzard:** None. **G.H. Diering:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.05

Topic: A.06. Developmental Disorders

Support: Lieber Institute for Brain Development
Pitt-Hopkins Research Foundation
NIH R01 grant 5R01MH110487 (BJM)
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MSCF Postdoctoral fellow grant (AIRM)

Title: TCF4 mutations cause dysregulation of the oligodendrocyte lineage in a human model of autism spectrum disorder

Authors: *A. ROMERO MORALES[1,2], G. SHIM[1], S. SRIPATHY RAO[1], S. M. STUMP[1], J. BOHLEN[1], B. J. MAHER[1,2,3];
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Abstract: Pitt-Hopkins Syndrome (PTHS) is a rare form of autism spectrum disorder characterized by severe developmental delay. PTHS is caused by *de novo* mutations in *TCF4*, a key transcription factor in multiple neurodevelopmental programs. Previous studies using PTHS mouse models have shown dysregulation in the density and maturity of oligodendrocytes (OL), resulting in myelination deficits; however, confirmation of these phenotypes in a human context is currently lacking. 2D differentiation of patient-derived hiPSCs into the OL lineage shows a reduction in the expression of several oligodendrocyte markers after 75 days in culture, including pan-OL marker *OLIG2* (CTRL vs PTHS, $p = 0.0001$) and *SOX10* (CTRL vs PTHS, $p < 0.0001$).

Progenitor markers *PDGFRa* (CTRL vs PTHS p<0.0001) and *CSPG4* (NG2, CTRL vs PTHS p=0.0006) were also reduced. Interestingly, this reduction was not due to impaired proliferation, as no difference in BrdU and Ki67 staining was observed. Additionally, neither cell death (via cleaved Caspase-3 staining) nor senescence (via p16INK4A staining) seems to be increased in the PTHS cell lines, suggesting a potential delay in OL cell fate specification in the mutant TCF4-derived oligodendrocyte precursor cells (OPCs). After induction of maturation (DIV 90), the expression of the pan-OL marker *SOX10* is significantly downregulated (Ctrl vs Haploinsufficiency p=0.0135, Ctrl vs Point mutant p=0.0254). Whereas the expression of the mature OL marker *MOG* (Ctrl vs PTHS haploinsufficiency p=0.9066, Ctrl vs PTHS point mutant p=0.0634) and the pre-myelinating marker *BCAS1* (Ctrl vs Haploinsufficiency p=0.0610, Ctrl vs Point mutant p=0.0658) shows a slight reduction in mRNA expression. Validation experiments using a 3D oligospheres (hOLS) model show a statistically significant reduction in the diameter of the spheres generated from the Haploinsufficiency lines (Ctrl vs PTHS haploinsufficiency p<0.0001). At DIV 100, SOX10 downregulation (CTRL vs PTHS, $p < 0.0001$) is observed, as well as a reduction in the expression of *PDGFRa*, *CSPG4*, *BCAS1* (Ctrl vs PTHS haploinsufficiency p=0.0244), *MBP*, and *MOG*. In addition, EM imaging of myelinated axons by DIV 200 shows abnormal patterns of myelination in the PTHS mutants. These results suggest TCF4 is a critical transcriptional regulator of OL lineage development and therefore predicts myelination deficits are a potential pathophysiological mechanism underlying neurodevelopmental abnormalities in PTHS.

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Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

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Presentation Number: NANO16.06

Topic: A.06. Developmental Disorders

Support: JSPS KAKENHI 23H02583
AMED 24bm1123039h0002

Title: Cross-species analyses reveal disrupted cortical hierarchy in Rett syndrome

Authors: R. LI[1,2], Y. ONUKI[3], S. TAKAHASHI[4], T. MATSUI[2], **A. ITO-ISHIDA**[1];
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Abstract: Rett syndrome is a neurodevelopmental disorder caused by mosaic loss of MeCP2, characterized by postnatal regression following initially normal development. Although studies in mouse models have linked synaptic alterations and local circuit dysfunction to behavioral

abnormalities, the circuit mechanisms driving this transition remain unknown.
We combined functional MRI in patients with wide-field calcium imaging in Mecp2-heterozygous (Mecp2-het) mice to identify a conserved reorganization of large-scale cortical networks. Our results showed a conserved and selective disruption of cortical hierarchical organization, anchored by the default mode network (DMN), while primary networks remained relatively intact. Notably, DMN segregation was reduced in Rett syndrome and correlated with motor impairment in both humans and mice.
To investigate the cellular mechanisms, we generated Mecp2-FlpO knock-in mice to specifically examine the networks formed by MeCP2-expressing and MeCP2-deficient neurons in Mecp2-het mice. We found that the network alterations were similarly present in both neuronal populations, suggesting that network dysfunction propagates across genetically distinct neurons via cell-extrinsic mechanisms.
Furthermore, we asked whether these network abnormalities are reversible through the restoration of MeCP2 expression. To achieve this, we developed an AAV vector incorporating a negative-feedback regulatory system to induce MeCP2 expression without causing excessive overexpression. Mecp2-het mice receiving the AAV showed improved motor performance. In parallel, their DMN characteristics shifted toward wild-type, indicating that higher-association network organization is reversible and coupled to functional recovery.
Together, these findings reveal a cell-extrinsic mechanism by which mosaic MeCP2 loss destabilizes cortical functional hierarchy, providing a systems-level explanation for how mosaic MeCP2 loss links to postnatal regression in Rett syndrome.

Disclosures: R. Li: None. **Y. Onuki:** None. **S. Takahashi:** None. **T. Matsui:** None. **A. Ito-Ishida:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.07

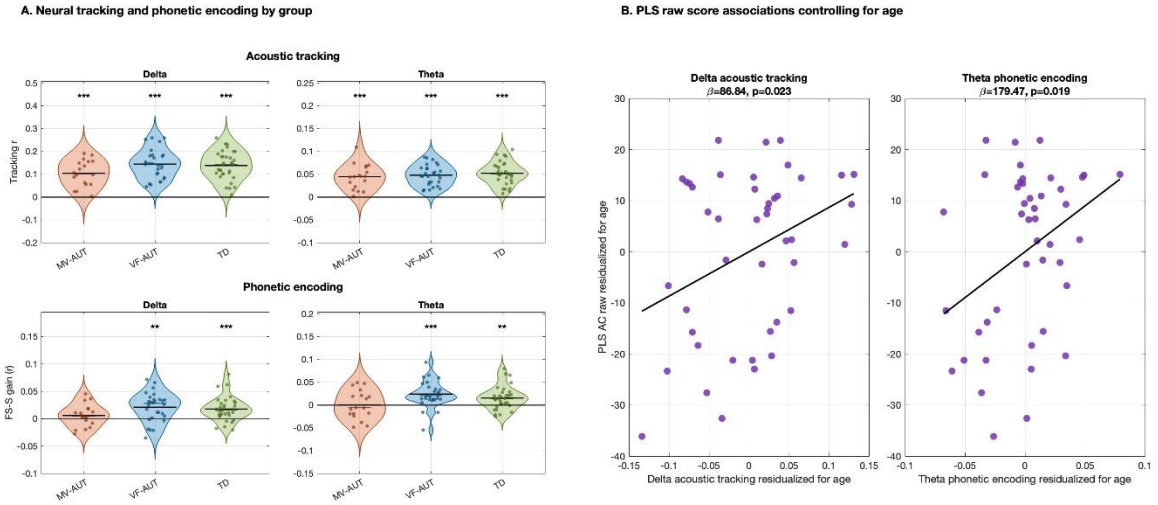
Topic: A.06. Developmental Disorders

Support: National Institute on Deafness and Other Communication Disorders (NIDCD) (P50 DC018006, MPIs: Tager-Flusberg/Kasari

Title: Cortical speech processing reveals intact acoustic tracking but impaired phonetic encoding in minimally verbal autistic children

Authors: *S. SUNDAR[1], W. AN[2], Y. CHEN[3], H. TAGER-FLUSBERG[4], C. A. NELSON[5], C. L. WILKINSON[2];
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Abstract: One-third of school-aged autistic children are minimally verbal (MV-AUT), but they are understudied due to difficulties in administering language assessments. As phonetic inventory predicts language outcomes in autism, we investigated if MV-AUT cortical speech encoding reflects altered acoustic or phonetic processing. We used temporal response function (TRF) modeling of EEG recorded from MV-AUT (n=18), verbally fluent autistic (VF-AUT, n=28), and typically developing (TD, n=32) children (ages 4-7) during passive listening to spoken nursery rhymes. Low-level acoustic tracking was assessed via backward TRF models reconstructing the speech envelope, and higher-order phonetic processing was assessed via forward models testing whether phonetic features improved EEG prediction beyond an acoustic baseline, both in delta (1-4 Hz) and theta (4-8 Hz) bands. Groups were compared using linear regression controlling for age, reporting q values (false discovery rate corrected). Acoustic tracking was above zero in all three groups across all bands (all $p<0.001$) with no significant group differences ($q=0.194$) despite numerically reduced delta acoustic tracking in MV-AUT. In contrast, phonetic-feature encoding was significantly above zero in TD and VF-AUT children (all $p<0.001$) but undetectable in MV-AUT children (delta $p=0.286$, theta $p=0.913$). We found significant group differences in both delta and theta bands ($q=0.048$), with MV-AUT children marginally reduced relative to TD ($q=0.097$) and VF-AUT children indistinguishable from TD. Within autistic children, delta acoustic tracking ($p=0.023$) and theta phonetic encoding ($p=0.019$) each predicted receptive language (Preschool Language Scales), controlling for age. Our findings suggest that MV-AUT children track speech acoustics normally but show reduced cortical encoding of phonetic features, locating their difference at a higher-order rather than general auditory stage. As both measures predicted receptive language, TRF-derived speech tracking may serve as a neural marker of language ability and intervention target.



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Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

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Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.08

Topic: A.06. Developmental Disorders

Title: Critical roles for Wac in glutamatergic progenitors during cortical development

Authors: *D. PACHECO CRUZ[1], X. SERRANO VELÁZQUEZ[3], G. S. CORREA[4], Z. FERNANDEZ[2], A. M. STAFFORD[5], C. QIAN[6], A. S. NORD[8], D. VOGT[7];
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Abstract: The WW-domain containing adaptor with coiled-coil gene (*Wac*) gene has putative roles in cell cycle regulation, autophagy, and transcriptional regulation. Mutations in the *Wac* gene cause DeSanto-Shinawi Syndrome (DESSH), an ultrarare neurodevelopmental disorder that presents with neurological complications such as developmental delay, ID, ADHD, and autism spectrum disorder (ASD). While *Wac* is a high-confidence ASD gene, previous studies have primarily been performed in cell lines and invertebrate models, and there is a lack of data on the role of *Wac* in neurons during cortical development. My lab previously developed a *Wac* heterozygous loss-of-function mouse model that exhibits susceptibility to seizures, relevant behavioral changes, and sex-specific alterations in brain volume. However, constitutive knockouts were embryonic lethal. Thus, to better understand the role of *Wac* during cortical development, I generated an *Emx1-Cre* conditional loss-of-function model to delete *Wac* in glutamatergic cortical neuron and glia progenitors. *Emx1-Cre* conditional KOs are viable and exhibit dramatic morphological phenotypes, including agenesis of the corpus callosum, delamination of the hippocampus, cortical disorganization and delamination, ventriculomegaly, and microcephaly. Here, I will describe the molecular, cellular, and morphological phenotypes due to *Wac* loss of function during cortical development. Importantly, I focus on developmental ages when critical events like proliferation, cell death, migration, and initial cell fate are established to fully understand the postnatal phenotypes due to *Wac* loss of function. These studies will unveil novel roles for the ASD risk gene, *Wac*, during cortical development as well as determine how glutamatergic neurons contribute to DESSH syndrome pathology.

Disclosures: D. Pacheco Cruz: None. **X. Serrano Velázquez:** None. **G.S. Correa:** None. **Z. Fernandez:** None. **A.M. Stafford:** None. **C. Qian:** None. **A.S. Nord:** None. **D. Vogt:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

Location: WCC Rm 144

Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.09

Topic: A.06. Developmental Disorders

Title: Aberrant neural wiring of cortical pyramidal neurons brain-globally triggers pathogenesis of autism spectrum disorders (ASD)

Authors: *Y.-P. TANG;
Inst. of Neurolog. Disease, West China Sch. of Medicine, Sichuan University, Sichuan Univer, Chengdu, China

Abstract: ASD are a group of neurodevelopmental disorders, while the features of neurodevelopmental defects in the brain, as well as their pathogenic origins, still remain elusive. Here, we first validated our newly generated *Mycbp2* mutant mice a robust ASD model, and then documented a number of neurodevelopmental pathologies including mismatched arealization between the primary motor cortex (M1) and somatosensory cortex (S1), disorganized cortical laminations, and disarranged alignments of pyramidal neurons (cPNs), which were further characterized by poly-axons and certain specific axonal pathologies, in the M1/S1 of mutant mice. Interestingly, whole-brain single neuron-tracing revealed that the axonal innervations of cPNs from the M1/S1 all the way down to the brainstem in mutant mice were disorganized, compared to those in wild-type littermates. Importantly, d-MRI and rs-fMRI revealed that the structural and functional dysconnectivity in mutant mice was co-incident, and was largely consistent to the patterns of the changed axonal innervations. Surprisingly, certain patterns of functional dysconnectivity in mutant mice could be manifested in brains of ASD patients. These results, based on the structural and functional profiles at the brain-global level, and from animal models to human patients, have demonstrated that the disorganized cPNs innervation brain-globally, rather than locally, roots the pathogenesis of ASD.

Disclosures: Y. Tang: None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

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Presentation Number: NANO16.10

Topic: A.06. Developmental Disorders

Support: R01MH120513
R21MH132834
T32MH112507

Title: A Core Molecular Signature of CHD8 Haploinsufficiency Emerges Across Diverse Neurodevelopmental Contexts

Authors: *N. SEBAN[1], C. P. CANALES[2], M. TABBAA[3], K. CICHEWICZ[4], A. S. NORD[5]; [1]Univ. of California Davis Neurosci. Grad. Program, Davis, CA; [2]CENTER FOR NEUROSCIENCE, Univ. of California Davis, Davis, CA; [3]Res. on Children, Youth and Families, USC, Los Angeles, CA; [4]UC Davis, Davis, CA; [5]Genomics Div., Univ. of California, Davis, Davis, CA

Abstract: Pathogenic variants in CHD8 represent one of the most penetrant genetic contributors to autism spectrum disorder (ASD). Although mouse models of Chd8 haploinsufficiency recapitulate many features observed in affected individuals, including alterations in brain development, gene regulation, and behavior, phenotypic outcomes have differed considerably among studies. To distinguish robust consequences of Chd8 deficiency from those influenced by experimental context, we performed a cross-study analysis spanning multiple mouse models, developmental time points, and genetic backgrounds. By integrating single-cell transcriptomic and chromatin accessibility profiling from embryonic (E14.5) and early postnatal (P2) forebrain, we identified recurrent disruptions in cell type-specific transcriptional and epigenetic programs, along with changes in cellular composition affecting populations previously implicated in the adult cortex. Comparative bulk and single-nucleus RNA sequencing analyses across distinct genetic backgrounds revealed substantial variability in pathways associated with progenitor proliferation and neuronal differentiation, demonstrating the contribution of genetic context to developmental outcomes. Despite these context-dependent effects, we identified a conserved molecular signature of Chd8 haploinsufficiency that was maintained across developmental stages, brain regions, cell types, genetic backgrounds, and species. In contrast, cellular phenotypes showed much greater dependence on developmental and regional context. To further explore this molecular signature we integrated our findings with an existed mouse brain Perturb-seq dataset profiling the cell type-specific effects of 2000 gene perturbations in the adult mouse brain. This allowed us to identify other pathogenic mutations that show correlated dysregulation of these genes in the brain as well as identify co-expression networks involving these genes. These findings suggest that conserved molecular alterations may provide a unifying framework for understanding downstream cellular phenotypes and may serve as candidate biomarkers for evaluating therapeutic interventions. More broadly, this work advances our understanding of how CHD8 deficiency disrupts neurodevelopment and illustrates the value of incorporating genetic diversity into preclinical models to better capture both the heterogeneity and shared molecular features of ASD.

Disclosures: N. Seban: None. **C.P. Canales:** None. **M. Tabbaa:** None. **K. Cichewicz:** None. **A.S. Nord:** None.

Nanosymposium

NANO16: Autism: Synaptic and Cellular Mechanisms

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Time: Monday, November 16, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO16.11

Topic: A.06. Developmental Disorders

Support: 1RM1MH138309-01

Title: A large-scale spatial and single-nucleus transcriptomic mapping of neurodevelopmental and psychiatric disorder risk-gene perturbations in the developing mouse brain

Authors: P. PALANISAMY[1], M. RAJAGOPALAN[2], V. ROY[3], T. LEACH[4], Y. KULKARNI[3], D. PARMAKSIZ[7], I. E. BJERKE[8], C. BERGER-LIEDTKA[5], S. MURRAY[10], Y. KIM[9], V. KUMAR[6], ***A. PAUL**[1];
[1]Neurosci. and Exptl. Therapeut., Penn State Col. of Med., HERSHEY, PA; [2]Neurosci. and Exptl. Therapeut., [3]Penn State Col. of Med., Hershey, PA; [4]Jackson Lab., Bar Harbor, ME; [5]Jackson Lab., Lamoine, ME; [6]Neurosci., Jackson Lab., Bar Harbor, ME; [7]Penn State Hershey Col. of Med., Hershey, PA; [8]Col. of Med., [9]Neural and Behavioral Sci., Penn State Univ., Hershey, PA; [10]The Jackson Lab., Bar Harbor, ME

Abstract: Neurodevelopmental and psychiatric disorders (NPDs) are genetically heterogeneous, yet many clinically distinct syndromes may converge on shared disruptions of brain cell-type maturation, spatial organization, and gene-regulatory programs. A major barrier has been the lack of standardized, cross-gene datasets that compare multiple NPD-risk perturbations across developmental stage, sex, cell type, and anatomical context. As part of the SSPsyGene Consortium Project SING effort, we are generating a coordinated single-nucleus and spatial transcriptomic resource from mouse knockout models of approximately 100 high-confidence Neuropsychiatric Disorder (NPD)-risk genes, including genes involved in chromatin regulation, synaptic signaling, cell adhesion, ion-channel function, translational control, mTOR signaling, and glial/lysosomal biology. Brains are collected at P14 and P56 from male and female mice to capture early postnatal circuit maturation and young-adult cellular organization. We are combining snRNA-seq with MERSCOPE/MERFISH imaging of coronal brain sections to define how loss of NPD-risk genes alters cell-type composition, cell-state maturation, and spatially resolved transcriptional programs. snRNA-seq will identify genotype-dependent changes in excitatory neurons, inhibitory interneurons, glia, and vascular-associated populations, while MERFISH will preserve anatomical context and map vulnerable cell populations across intact brain tissue. Using integrated cell-type annotation, differential expression, gene-set, gene module analysis, and cross-gene comparison, we will define cell-type-specific vulnerability signatures and ask whether genetically diverse NPD models converge on recurrent molecular programs or produce distinct functional-class-specific phenotypes. Initial data generation is underway as well as establishing a scalable framework for identifying shared and divergent cellular consequences of NPD-risk gene loss in the developing mouse brains.

Disclosures: P. Palanisamy: None. **M. Rajagopalan:** None. **V. Roy:** None. **T. Leach:** None. **Y. Kulkarni:** None. **D. Parmaksiz:** None. **I.E. Bjerke:** None. **C. Berger-Liedtka:** None. **S. Murray:** None. **Y. Kim:** None. **V. Kumar:** None. **A. Paul:** None.

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.01

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

Support: Johns Hopkins University Catalyst Award
NIH/NIA 1R01AG071512

Title: Neuroprotective roles of heme catabolism mediated by biliverdin reductase A in Alzheimer's disease

Authors: *B. D. PAUL;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Biliverdin reductase A (BVRA), the terminal enzyme in heme catabolism, produces bilirubin, a neuroprotective lipophilic antioxidant. Here, we identify a nonenzymatic role for BVRA in redox regulation. Using phylogenetic, genetic, biochemical, and enzymatic approaches, we show that BVRA possesses critical antioxidant activity independent of its catalytic function. Transcriptomic analyses further reveal that BVRA physically and genetically interacts with nuclear factor erythroid 2-related factor 2 (NRF2), a key regulator of cellular redox signaling. ChIP-seq and RNA-seq data indicate that BVRA and NRF2 coordinately regulate antioxidant genes, many of which are dysregulated in neurodegenerative disease, including Alzheimer’s disease. Together, these findings define a noncanonical BVRA-NRF2 axis that supports neuroprotection and position BVRA as a dual-function integrator of antioxidant defense across lipophilic and hydrophilic compartments in the brain.

Disclosures: B.D. Paul: None.

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.02

Topic:

Support: NIH Grant R21AG084065

Title: Green Tea EGCG: A Natural Therapeutic Agent in Alzheimer's Disease Targeting the CDK5 and CRMP2 Pathway

Authors: *N. SRIKUMAR[1], M. IANNUCCI[2], A. SAHOO[2], M. BUCK[2];
[1]Princeton Univ., Princeton, NJ; [2]Case Western Reserve Univ., Cleveland, OH

Abstract: Alzheimer’s Disease is a neurodegenerative disorder characterized by the hyperphosphorylation of Tau and collapsin response mediator protein-2 (CRMP2), a newly identified and understudied biomarker. Hyperphosphorylation of these proteins is caused by deregulated cyclin-dependent kinase-5 (CDK5) function. This increased phosphorylation activity

leads to neurofibrillary tangles, partially composed of hyperphosphorylated CRMP2, that cause a loss in neuronal synaptic communication. Thus, CRMP2 and CDK5 are potential targets to alleviate Alzheimer's Disease symptoms. However, there is a lack of consensus on the molecular basis of Alzheimer's, leading to inadequate treatment. Epigallocatechin-3 gallate (EGCG), a green tea catechin, has neuroprotective properties against inflammation of neural tissue and is an emerging medicinal herb with promising results. The objective of this study is to identify the molecular interactions of EGCG with CDK5 and CRMP2. Microscale thermophoresis (MST) was performed to understand binding affinities, while kinase assays and western blotting were used to understand phosphorylation patterns of CDK5 in the presence of CRMP2 and EGCG. Mass spectrometry was performed to validate CRMP2's phosphorylation sites. Computational docking was conducted using ClusPro and AutoDock Vina to understand protein conformations and EGCG binding regions. It was concluded through MST that CDK5 and CRMP2 have a strong binding affinity that is disrupted in the presence of EGCG. Using a Michaelis-Menten kinetic analysis, the results revealed that EGCG is an uncompetitive inhibitor, as noted by the reduction in Km and Vmax values. The efficacy of EGCG in reducing CDK5-induced phosphorylation was heightened in the presence of both CDK5 and CRMP2 compared to phosphorylation assays between EGCG and CDK5. Preliminary computational models appear to corroborate the experimental results to reveal CDK5's interaction with CRMP2's C-terminus and EGCG's binding pockets near CRMP2's Arginine 173, a positive pocket, and CDK5's Lysine 33, the ATP-binding region pocket. It was concluded that the CDK5 and CRMP2 interaction is impacted by the uncompetitive inhibitor, EGCG. Overall, this study highlights the specificity of EGCG to the CDK5-CRMP2 complex in Alzheimer's Disease.

Disclosures: N. Srikumar: None. **M. Iannucci:** None. **A. Sahoo:** None. **M. Buck:** None.

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

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Presentation Number: NANO17.03

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

Support: BrightFocus Award A2025013S
Alzheimer's Association Zenith Award 26-1447450
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NIH Grant P0544014
NIH/NIA Grant R01AG057234
National Institutes of Health (NIH) S10 RR028962

Title: Resilience to neuronal hyperactivity and restoration of the neuroimmune interactome and decision-making by blocking fibrin in a model of Alzheimer's disease

Authors: *Z. YAN[1], A. MENDIOLA[4], K. LAUDERDALE[2], K.-Y. KIM[5], Y. YONG[1], K. LENG[6], E. BUSHONG[7], R. SCHUCK[1], A. MEYER-FRANKE[1], A. AGRAWAL[8], N. GILL[1], R. THOMAS[1], J. KELLER[9], D. C. BALLARD[10], M. MADANY[11], J. SIMMS[1], R. TOGNATTA[1], P. ALZAMORA[1], K. PIERSON[3], N. KARVELAS[12], K. HAN[14], J. RYU[15], B. MILLER[16], F. ELAHI[13], M. H. ELLISMAN[17], J. J. PALOP[18], K. AKASSOGLOU[19];
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Abstract: Cerebrovascular pathology and neuronal network dysfunction are early features of Alzheimer's disease (AD) associated with cognitive decline, but the vascular and immune triggers of neuronal hyperactivity remain largely unknown. Here, we show that the blood coagulation factor fibrin, deposited in the AD brain, promotes neuronal hyperactivity and disrupts the microglia-neuron interactome in an AD mouse model. To examine the effect of fibrin-induced immune activation in AD, we crossed 5XFAD mice with $Fgg^{\gamma 390\text{-}396A}$ mice, which express a mutant fibrinogen γ chain lacking the fibrin-CD11b binding inflammatory domain while retaining normal clotting function. By *in vivo* two-photon imaging of neuronal calcium indicator jRCaMP1b and GFP-labeled microglia ($Cx3cr1^{GFP}$) in awake mice, we show that fibrin drives microglia-mediated neuronal hyperactivity, network hypersynchrony, and suppressed dynamic microglial brain surveillance. Multimodal imaging co-registering confocal microscopy and serial block-face electron microscopy with 3D reconstruction, identified that genetic blockade of fibrin-inflammatory domain restored microglial contacts with neurons in AD mice. We employed a cost-benefit conflict paradigm to assess decision-making and found that blockade of fibrin inflammatory domain protected against high-risk decision-making in 5XFAD mice. Using snRNA-seq combined with unbiased ligand-receptor interaction and cell-cell communication analyses, we identified widespread fibrin-dependent transcriptional alterations in glial cells and in excitatory and inhibitory neuronal populations. Integration of microglial and neuronal transcriptional signatures further revealed fibrin-dependent disruption of innate immune and glutamatergic signaling between microglia and neurons in AD mice. Finally, unbiased SomaScan proteomic profiling of 7,000 analytes in the cerebrospinal fluid from AD patients revealed correlations between CSF fibrinogen levels and biomarkers of inflammation, vascular

dysfunction, and synaptic injury. Thus, resilience to neuronal hyperactivity and restoration of the neuroimmune interactome by targeting fibrin may have therapeutic implications for Alzheimer's disease and related conditions.

Disclosures: Z. Yan: None. **A. Mendiola:** None. **K. Lauderdale:** None. **K. Kim:** None. **Y. Yong:** None. **K. Leng:** None. **E. Bushong:** None. **R. Schuck:** None. **A. Meyer-Franke:** None. **A. Agrawal:** None. **N. Gill:** None. **R. Thomas:** None. **J. Keller:** None. **D.C. Ballard:** None. **M. Madany:** None. **J. Simms:** None. **R. Tognatta:** None. **P. Alzamora:** None. **K. Pierson:** None. **N. Karvelas:** None. **K. Han:** None. **J. Ryu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gladstone Institutes (patents 9,669,112; 10,451,611; 11,573,222), Therini Bio (stock options). **B. Miller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cambridge University Press (royalty), Elsevier, Inc. (Royalty), Guilford Publications, Inc. (Royalty), Johns Hopkins Press (Royalty), Oxford University Press (Royalty), Taylor & Francis Group (Royalty). F. Consulting Fees (e.g., advisory boards); Bluefield Project to Cure FTD (Scientific Advisory Board), the John Douglas French Alzheimer's Foundation (Scientific Advisory Board), Fundación Centro de Investigación Enfermedades Neurológicas, Madrid, Spain (Scientific Advisory Board), Genworth, Inc (Scientific Advisory Board), the Kissick Family Foundation (Scientific Advisory Board), the Larry L. Hillblom Foundation (Scientific Advisory Board), NKGen Biotech, Inc. (Scientific Advisory Board), Tau Consortium of the Rainwater Charitable Foundation (Scientific Advisory Board). Other; Neurocase (editor), Frontiers in Neurology (section editor). **F. Elahi:** None. **M.H. Ellisman:** None. **J.J. Palop:** None. **K. Akassoglou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Therini Bio (founder; pending patent US18/571,096), Akodio Therapeutics (founder), University of California (patents 7,807,645; 8,569,242; 8,877,195; 8,980,836), Gladstone Institutes (patents 9,669,112; 10,451,611; 11,573,222). F. Consulting Fees (e.g., advisory boards); Therini Bio (consultant).

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.04

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

Support: Alzheimer's Association

Title: Cognitive Function Improves in Alzheimer's Disease Mice Following Pharmacological Reduction of Plasma BCAAs

Authors: *M. ALIAHMADI, Z. HAQUE, M. RAMEZAN, N. RAMONI, F. DASHTI, A. C. SHIN;
Texas Tech. Univ., Lubbock, TX

Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no effective cure. Our laboratory has identified a positive association between elevated circulating branched-chain amino acids (BCAAs) and AD and previously demonstrated that BCAAs impair neuronal function while BCAA-lowering intervention BT2 alleviate AD-related pathology. However, the optimal dose of BT2 and its underlying mechanisms remain unknown. **Methods:** To determine the most effective dose of BT2 in AD pathology and cognitive function, we conducted a follow-up study using 3-month-old wildtype (WT) and 5xFAD female mice (n= 7 per group). Animal were divided into ten groups: WT, WT + BT2 (20, 40, and 80 mg/kg BW), WT + WT + BCAA restriction diet (50%), 5xFAD, 5xFAD + BT2 (20, 40, and 80 mg/kg BW), 5XFAD + BCAA restriction diet (50%). BT2 was administered via daily intraperitoneal injection for 30 consecutive days. At the end of the treatment, plasma was collected for BCAA quantification using a BCAA assay. Cortical tissue was collected for gene expression analysis by RT-qPCR, protein analysis by Western blot, and mitochondrial complex I activity measurement using an assay kit. Cognitive function was also assessed using Y-maze before and after treatment and Morris Water Maze (MWM) after treatment. **Results:** BT2 treatment reduced Plasma BCAA level in all AD groups after one month. Notably, 5xFAD mice treated with BT2 at 40 mg/kg or a BCAA restriction diet showed significant improvement in the scape latency (MWM). Consistent with these findings, 5xFAD mice treated with (40 mg/kg) showed a maintained spontaneous alternation in Y-maze, whereas other AD groups exhibited a decline. RT-qPCR analysis showed that 40 mg/kg BT2 tended to reduce cortical expression of genes involved in BCAA metabolism and amyloidogenic pathways. These findings were consistent with Western blot results showing a reduced pBCKDH/BCKDH ratio, suggesting enhanced BCKDH activity in 5xFAD mice treated with 40 mg/kg BT2. Interestingly, BT2 treatment altered mitochondrial complex I activity in 5xFAD mice, with the 40 mg/kg dose that appears to restore a more balanced mitochondrial metabolic state. **Conclusion:** Our findings demonstrate that the BCAA-lowering compound BT2 has the potential to mitigate cognitive decline in AD. The observed improvement in cognitive performance, accompanied by reduced plasma BCAA, enhanced BCKDH activity, favorable changes in gene expression, and mitochondrial complex I activity, underscores BT2's therapeutic promise. These results suggest that targeting BCAA metabolism may represent a novel strategy for slowing AD progression.

Disclosures: M. Aliahmadi: None. **Z. Haque:** None. **M. Ramezan:** None. **N. Ramoni:** None. **F. Dashti:** None. **A.C. Shin:** None.

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.05

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

Title: Metabolic and morphological effects of pro-inflammatory THP-1 macrophage secretions on differentiated SH-SY5Y, and intervention by peptoid JPT1

Authors: *M. J. KAVEN, M. A. MOSS;
Biomed. Engin., Univ. of South Carolina, Columbia, SC

Abstract: Alzheimer's disease (AD) is the seventh leading cause of death in the US, hallmarked by amyloid-β (Aβ) plaques, tau neurofibrillary tangles, and accumulation of pro-inflammatory cytokines. Peptoid JPT1 is a dual-target therapeutic with modular design. Its core sequence mimics Aβ in a manner designed to bind to Aβ peptides, and JPT1 demonstrates inhibitory effects on Aβ aggregation. JPT1 also binds to membrane-bound receptors abundant in microglia and neurons that regulate brain inflammation, attenuating the LPS-induced release of pro-inflammatory cytokines IL-1β, IL-6, and IL-8 by macrophages. Investigating the effects of this attenuation on neuronal toxicity and morphology following neuronal treatment with pro-inflammatory conditioned media (CM) provides additional evidence for potential of JPT1 in AD management. Quantified by caspase-3/7 apoptosis, lactate dehydrogenase (LDH) release, and XTT viability assays, and imaged by confocal microscopy (Leica Stellaris™ 8 FALCON), the results illuminate new understanding of neurodegeneration mediated by inflammation in vitro.
Human THP-1 monocytes (ATCC™) are differentiated into macrophages via phorbol 12-myristate 13-acetate (PMA, 3d) before incubation (3d) with media alone, media containing LPS, or media containing LPS and JPT1. The CM groups produced - CM, LPS CM, and LPS+JPT1 CM - are harvested and stored at -80ºC.
Human neuroblastoma SH-SY5Y (Sigma™) are differentiated by retinoic acid (4d) followed by PMA (3d) to render a dopaminergic, neuronal-like phenotype. These cells are treated with THP-1 CM for 24 h (caspase-3/7) or 5 d (LDH, XTT, confocal imaging). All results include 4 independent experiments, at minimum. Statistical analyses are performed via one-way ANOVA with Tukey post-hoc. Significance is defined by $p<0.05$.
Differentiated SH-SY5Y treated for 24 h with LPS+JPT1 CM are less apoptotic than those treated with LPS CM prepared without JPT1 intervention ($p<0.05$), by measure of caspase-3/7 activity. After 5 d treatment, the LPS+JPT1 CM group exhibits less damage to the neuronal membrane than the LPS CM group ($p<0.05$), by measure of LDH release. Together, these results suggest therapeutic properties of JPT1 that may help to combat immunological dysregulation in the brain and its associated neuronal pathologies.

Disclosures: M.J. Kaven: None. **M.A. Moss:** None.

Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.06

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

Support: R01AG073377

Title: DDL-110, A Brain-Permeable Candidate Drug sAPPalpha Enhancer with a Novel Mechanism of Action for Alzheimer's Disease

Authors: *P. SPILMAN[1], J. CAMPAGNA[2], C. ZHU[3], D. E. BREDESEN[4], V. JOHN[2];
[1]Mary S Easton Ctr. For Alzheimer's Dis. Res. and Care, Los Angeles, CA; [2]Neurol., [3]Dept Neurol, UCLA, Los Angeles, CA; [4]Neurol., UCLA, Novato, CA

Abstract: Background. The most recent advancement in therapy for Alzheimer's disease (AD) is the approval of amyloid-beta (Abeta)-directed antibodies. While these antibodies reduce plaque load in brain tissue with a few infusions, they only slow cognitive decline and do not reverse other AD-related tissue damage. Thus there is a critical need for new therapeutics that target neuronal circuits, restore neuronal function, and improve memory. Enhancement of soluble Amyloid Precursor Protein alpha (sAPPalpha), product of alpha-secretase cleavage of APP, has the potential to exert neurotrophic pro-cognitive effects due to its reduction of Abeta by inhibition of BACE1, reduction of neurofibrillary tangles (NFTs - another pathological hallmark of AD brain tissue) by inhibition of GSKbeta phosphorylation of tau, and support of synapses/neurites. We previously reported our identification of F03 (tropisetron), an orally-available brain-permeable small molecule that increases sAPPalpha in neuronal cell lines and in murine models of AD. Here we report our discovery of DDL-110, a more potent sAPPalpha enhancer analog of F03 that can target neuronal circuits and improve memory. DDL-110 has a favorable IND studies profile and has potential for further clinical development. **Methods**. We utilized iterative medicinal chemistry to design NCE analogs of F03 and assessed the potency of these compounds for sAPPalpha enhancement in both neuronal SH-SY5Y cells and Chinese Hamster Ovary cells stably transfected with human APP (CHO-7W). Mechanistic studies were performed to reveal potential direct targets of compounds. The most potent analog, DDL-110, underwent in vivo pharmacokinetic (PK) analysis and efficacy testing in multiple studies including two murine models of AD and both younger (5-7 months) and older (11 months or greater) mice. Behavior and working memory were assessed Novel Location Recognition (NLR) and Novel Object Recognition (NOR). Brain tissue was collected for determination of sAPPalpha, sAPPbeta, and Abeta1-40 and 1-42. Further, DDL-110 underwent advanced IND-enabling preclinical testing, including ADME-T and toxicity studies in rat and dog. **Findings.** DDL-110 is a more potent analog of F03 with good drug-like properties and oral brain permeability that displays enhanced efficacy in vivo, including greater increase in sAPPalpha in brain and improvement of memory in aged AD model mice. Mechanistic studies suggest DDL-110 exerts its effects by a novel mechanism to be discussed in the presentation. IND-enabling studies revealed low toxicity and support the continued development of DDL-110 toward clinical testing for AD.

Disclosures: P. Spilman: None. **J. Campagna:** None. **C. Zhu:** None. **D.E. Bredesen:** None. **V. John:** None.

Nanosymposium

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Presentation Number: NANO17.07

Topic:

Support: The Valour Foundation
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Rebecca E. Barchas MD DLFAPA Case Western Reserve University
Professorship in Translational Psychiatry
Morley-Mather Chair in Neuropsychiatry
Louis Stokes VA Medical Center resources and facilities
Department of Defense Peer-Reviewed Alzheimer's Research Program (PRARP)
Award AZ210092 (W81XWH-22-1-0129)

Title: Investigating how acetylated tau contributes to the higher risk of Alzheimer's disease following traumatic brain injury

Authors: *V. Q. INDRAKUMAR[1], E. VAZQUEZ-ROSA[2], S. BARKER[3], C. CINTRON[2], K. FRANKE[2], L. DOU[4], L. GAN[5], F. CHENG[4], A. A. PIEPER[2];
[2]Psychiatry, [3]Pathology, [1]Case Western Reserve Univ., Cleveland, OH; [4]Cleveland Clin., Cleveland, OH; [5]Brain and Mind Res. Inst., Weill Cornell Med., New York, NY

Abstract: Traumatic brain injury (TBI) is the most significant environmental risk factor for Alzheimer's disease (AD), and the third greatest risk factor overall. Although it is well established that TBI accelerates the onset and severity of AD, the mechanisms behind this process are unknown. We have recently shown that TBI increases the accumulation of acetylated tau (ac-Tau) in the brain, specifically on two lysine residues. This non-canonical pathological signaling pathway leads to axonal degeneration, cognitive impairment, and eventual neuronal cell death, and we have shown that reduction of ac-Tau is neuroprotective after TBI. AD is also associated with higher levels of ac-Tau in the brain, leading us to investigate whether ac-Tau was mechanistically involved in TBI-mediated acceleration of AD. In conjunction with the 5xFAD mouse model of AD, we applied a clinically relevant multimodal TBI model that mimics key features of human TBI. Applying mild TBI to 5xFAD mice resulted in significantly accelerated cognitive decline, amyloid plaque accumulation, microgliosis, blood-brain barrier (BBB) deterioration, and neurodegeneration compared to 5xFAD mice that did not undergo TBI. The same pathology was not observed in wild-type littermates that had mild TBI. Utilizing either the P300/CBP inhibitor diflunisal or the energy-stabilizing molecule P7C3-A20 reduced ac-Tau and blocked TBI-induced acceleration of AD symptoms. Clinical data revealed that TBI patients who were taking potent P300/CBP inhibitors had a significantly lower risk of later developing dementia. Our results establish ac-Tau as a key driver of TBI-induced acceleration of AD and lay the groundwork for drug intervention for this condition.

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Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.08

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

Support: AARGD-24-1313648
NIGMS Grant 2T32GM132055

Title: Improving lysosomal function enhances the efficacy of a novel TREM2 agonistic antibody

Authors: *C. A. MARTINEZ, P. DA SILVA FROST, J. MCWHIRT, J. H. LEDO;
Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Alzheimer's Disease (AD) is a progressive, incurable neurodegenerative disease characterized by the accumulation of amyloid-β (Aβ) peptide, hyperphosphorylated tau aggregation, and chronic neuroinflammation. Microglia, the parenchyma's resident immune population, play a central role by clearing Aβ from the brain, but also contribute to disease progression through aberrant pruning and maladaptive immune activation. Therapeutic strategies aimed at reducing Aβ pathology have recently achieved clinical milestones, with several anti-amyloid antibodies receiving FDA approval. However, their cognitive benefit remains modest and is frequently accompanied by amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhage. TREM2 is a genetically validated and biologically attractive therapeutic target to regulate microglial activity, but TREM2 agonists tested alone have shown limited efficacy in preclinical models and failed to demonstrate significant benefit in clinical trials. These limitations suggest that enhanced Aβ phagocytosis may be insufficient to achieve meaningful therapeutic effects. Notably, AD microglia exhibit pronounced lysosomal dysfunction due to impaired autolysosome acidification mechanisms linked to several AD risk factors, including the *APOE4* allele. *We hypothesize that impaired degradation of phagocytosed Aβ represents a critical bottleneck limiting microglia-mediated clearance and anti-TREM2 therapeutic efficacy.* To investigate this hypothesis, we tested individual versus combined treatment with AbTr1, a novel TREM2 agonistic antibody that we developed, and C1, an activator of Transcription Factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy. Leveraging APOE4 iPSC-derived microglia (iMGs) with lysosomal dysfunction, we assessed whether these treatments enhanced Aβ phagocytosis and degradation. We found that AbTr1 treatment increases Aβ phagocytosis in a dose-dependent manner. However, preliminary data suggests the rate of degradation remains impaired, resulting in increased intracellular Aβ burden. When iMG were treated with C1, phagocytosis remains unchanged while degradation increases. Furthermore, pilot data indicates that AbTr1-C1 dual treatment engages complementary phagocytic and lysosomal pathways to increase extracellular and intracellular Aβ clearance. This combined strategy offers a framework to optimize therapeutic efficacy of TREM2 agonism, revealing a promising new avenue for AD therapeutics.

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Nanosymposium

NANO17: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Rm 146C

Time: Monday, November 16, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO17.09

Topic: I.04. Executive Functions

Title: Meta-analysis Demonstrates Therapeutic Exercise Has a Positive Overall Effect on Alzheimer's Disease Symptoms After 6 Months

Authors: *S. O. AHMAD[1], H. RAFIEI[1], D. L. STILES[1], B. KILCOYNE[2], S. PIETERS[1], J. GALVAN[3], C. POHL[4];
[1]St. Louis Univ., Saint Louis, MO; [2]St. Louis Univ., St Louis, MO; [3]St. Louis Univ., CHICAGO, IL; [4]St. Louis Univ., O'Fallon, MO

Abstract: Background: Alzheimer's Disease (AD) is the most prevalent form of Dementia, and a debilitating neurodegenerative disorder for millions worldwide. While there is no proven cure for AD, it is widely agreed upon that aerobic exercises and occupations can help slow the progression of the disease and maintain executive function. Research Question: This research article aims to compare the differences in outcomes of different forms of exercise on several Cognitive outcomes in Alzheimer's Disease, as evaluated by Meta-analysis. Methods: Key terms were AD and exercise terms. These search terms were then entered to electronic databases: Ovid MEDLINE, SCOPUS, and CINAHL in from January 2015 to November 2025. An ancestral bibliography was also performed. Results: Four reviewers screened the title and abstract records (n=1,732) found in the initial search. The review identified 18 studies which met inclusion criteria for meta-analysis. Results indicated no overall effect of therapeutic exercise on patients with AD over all of the studies when time wasn't a variable. The overall d-index was 0.045, The effect was not statistically significant with a CI95% of $-0.006842 < \mu < 0.09729$, $p > 0.05$, as the CI includes zero. However, when time was taken into account, results indicated a positive overall effect of therapeutic exercise on patients with AD after 6 months or more of treatment, where the overall d-index was 0.4001.

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Nanosymposium

NANO18: Human Audiovisual Integration

Location: WCC Rm 140

Time: Monday, November 16, 2026, 8:00 AM - 10:00 AM

Presentation Number: NANO18.01

Topic: E.08. Multisensory Integration

Support: National Natural Science Foundation of China 82171156
National Natural Science Foundation of China 32371051
Peking Union Medical College Hospital Talent Cultivation Program (Category C) No.UBJ10135

Title: A Different Pattern of Cross-modal Plasticity in Single-sided Deafness: Hypo-activation during Visual Processing and Enhanced Audiovisual Integration

Authors: *Y. SHANG;
Dept. of Otorhinolaryngology, Peking Union Med. Col. Hosp., Beijing, China

Abstract: Overwhelming studies in deafness observed cross-modal recruitment of the auditory cortex (AC) for visual processing, suggesting a redistribution of neural resources from auditory to other sensory modalities following complete auditory deprivation. However, how central resources are reallocated between visual and auditory modalities in individuals with partial auditory deprivation—a more prevalent condition—remains largely unclear. In individuals with single-sided deafness (SSD), an extreme case of partial auditory deprivation, our previous fMRI study observed downward cross-modal plasticity (decreased activation) of AC during visual working memory processing, in the opposite direction to bilateral deafness. We speculated that the increased cortical resource requirement for auditory processing due to reduced auditory input might be the reason; however, this has not been confirmed because of the lack of concurrent auditory task studies. To address this issue, we conducted an fMRI study using a 2-back paradigm including visual, auditory, and audiovisual-mixed conditions in 33 individuals with congenital SSD (left/right 15/18) and 25 normal-hearing (NH) controls. Behaviorally, the SSD group performed worse than the NH controls, showing reduced accuracy across all conditions, along with slower responses specifically in the audiovisual-mixed condition. During the visual task, the SSD group exhibited weaker activation in the visual cortex. In contrast, during the audiovisual-mixed task, the SSD group demonstrated stronger activation in AC and anterior cingulate cortex. However, no significant alteration was observed during the auditory task, despite reduced peripheral auditory input in SSD patients. Region of interest analysis for AC revealed that activation was decreased with marginal significance during the visual task, while no significant difference during the auditory task. Our findings indicate that in SSD, for higher-order unimodal processing, audition generally recruited comparable cortical resources, whereas vision allocated less. SSD patients did not exhibit the auditory-to-visual resource shift in AC that is typical in bilateral deafness, but instead allocated more resources to audiovisual integration. Enhanced audiovisual integration is a crucial compensatory pattern in SSD.

Disclosures: Y. Shang: None.

Nanosymposium

NANO18: Human Audiovisual Integration

Location: WCC Rm 140

Time: Monday, November 16, 2026, 8:00 AM - 10:00 AM

Presentation Number: NANO18.02

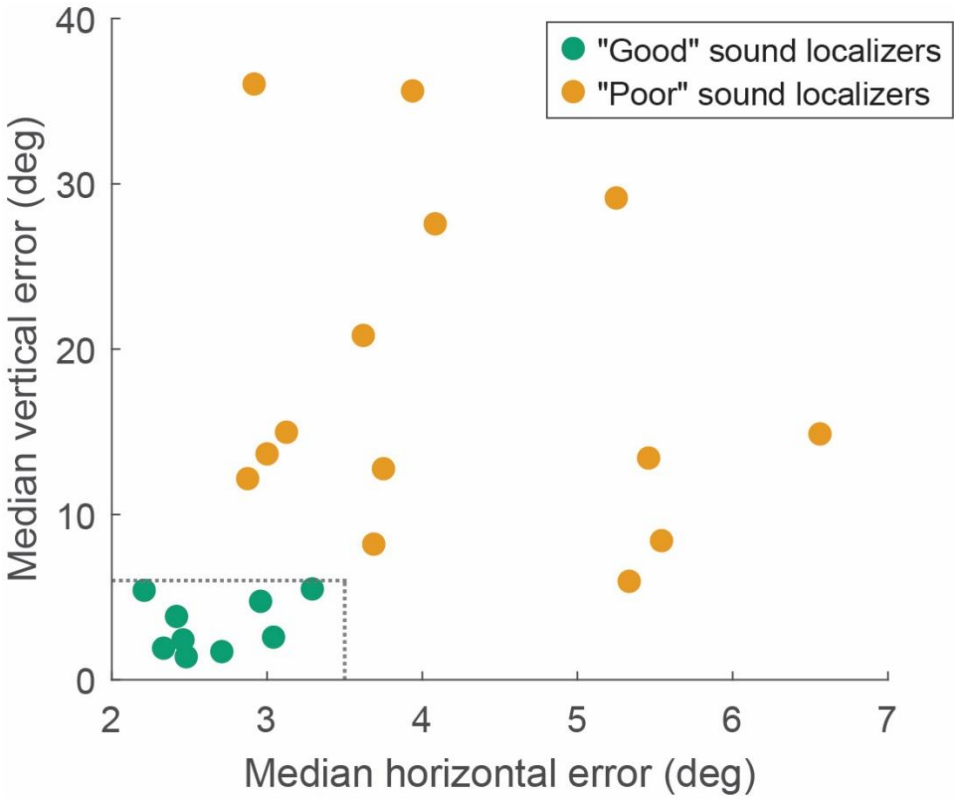
Topic: E.08. Multisensory Integration

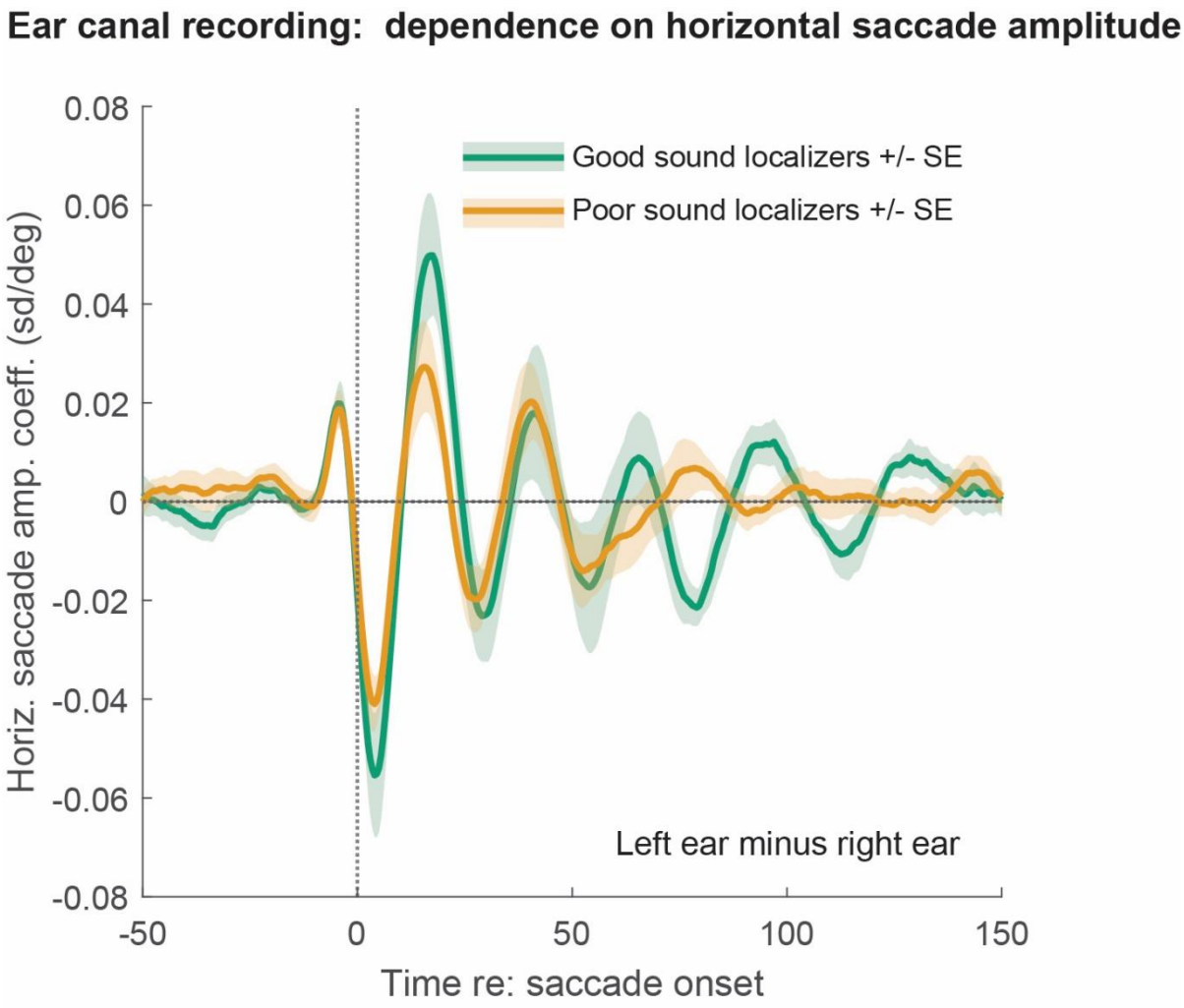
Support: NIH Grant DC020363

Title: Sound localization accuracy is correlated with the properties of eye movement-related eardrum oscillations (EMREOs)

Authors: *J. M. GROH, J. L. HERCHE, C. D. KING;
Duke Univ., Durham, NC

Abstract: Calibration of sound localization behavior in species with mobile eyes requires not only accurate visual input but also accurate oculomotor signals across the lifespan. The recent discovery of eye movement-related eardrum oscillations suggests that oculomotor signals may be incorporated into auditory processing at the level of the ear. One inference of this discovery is that individual variation in such signals might be correlated with individual variation in sound localization accuracy. Here, we tested this hypothesis in humans with normal hearing. We discovered that there is considerable variation in the accuracy of sound localization (here, saccades to sounds) even in normal individuals: median horizontal errors ranged from 2-6°, and median vertical errors could be as large as 36°. We separated the subject pool into groups with "good" performance (median vectorial error < 8°) vs "poor" performance (median vectorial error > 10°) and evaluated their respective EMREOs. The EMREOs differed across the two groups in both horizontal and vertical dimensions, in how saccade amplitude vs. initial eye position was encoded, and across time with respect to the saccade. These results are consistent with the interpretation that EMREOs are associated with underlying processes that ensure the accuracy of sound localization.





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Nanosymposium

NANO18: Human Audiovisual Integration

Location: WCC Rm 140

Time: Monday, November 16, 2026, 8:00 AM - 10:00 AM

Presentation Number: NANO18.03

Topic: E.08. Multisensory Integration

Title: Timing and distribution of superior temporal responses to electrical stimulation of human occipital cortex

Authors: *E. CUNNINGHAM, Y. LI, D. BRANG;
Psychology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: In natural environments, sounds are frequently accompanied by visual cues. These cues often carry information that can be used to refine the neural representation of auditory input (as when lip motion reduces ambiguity of speech in noise). Converging evidence from humans and nonhuman primates (NHP) suggests that visual influences on auditory processing result (in part) from intercommunication between sensory cortices. However, in humans, sources of visual input to auditory cortex remain difficult to isolate, given overlapping contributions from subcortical, visual cortical, and higher order polysensory areas. Here, our aim was to provide causal insight into the organization of human visual-to-auditory communication through examination of the effects of direct electrical stimulation of occipital cortex on responses in superior temporal gyrus (STG). We present a preregistered assessment of human corticocortical evoked potential (CCEP) responses derived from intracranial recordings in 23 patients with epilepsy, with a focus on the presence, timing, and magnitude of the initial response (N1 peak). Overall, occipital stimulation elicited STG responses at above-chance levels in 21/23 patients (average within-subject response rate: 25%; median response latency: 29ms), with an anterior-posterior gradient such that responses in posterior STG were typically faster, more frequent, and more robust than responses in anterior STG. Given NHP reports and the proposed role of visual input in speech comprehension, regions V1-V3, hMT+, and fusiform (anatomically defined) were targeted for detailed investigation. With respect to V1-V3, superior temporal responses were most prevalent and pronounced following stimulation of V2 (particularly over posterior STG), consistent with NHP observations (although with little evidence for eccentricity-dependent organization analogous to that observed in the NHP). With respect to hMT+ and fusiform, stimulation of both regions evoked a posterior-dominant STG response; However, stimulation of the fusiform produced markedly faster and more prevalent responses than stimulation of hMT+ (with estimated latencies of 23 ms vs. 42 ms, respectively). Generalized additive mixed models provided initial evidence that effects in the fusiform were spatially specific (relative to surrounding cortex), whereas evidence for specificity in hMT+ was limited. These results support preferential, rapid communication of visual input from fusiform cortex to STG, which may provide scaffolding for the relay of facial articulatory information during speech processing.

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Nanosymposium

NANO18: Human Audiovisual Integration

Location: WCC Rm 140

Time: Monday, November 16, 2026, 8:00 AM - 10:00 AM

Presentation Number: NANO18.04

Topic: E.08. Multisensory Integration

Support: NIH Grant DC016297

Title: Less than words: sublexical visual speech processing constrains lexical inference to make you understand

Authors: *A. NIDIFFER, D. HERNÁNDEZ-GUTIÉRREZ, E. C. LALOR;
Univ. of Rochester, Rochester, NY

Abstract: Human speech perception is largely underpinned by an auditory hierarchy where complex spectrotemporal speech patterns are carried through to meaning via a series of linguistic transformations. Seeing a speaker's face endows us with a range of benefits that ultimately boosts speech comprehension. Improvements to selective attention and acoustic processing are thought stem from redundant audiovisual dynamics. Other findings such as the McGurk Effect and the existence of unique auditory, visual, and audiovisual lexical neighborhoods suggest that based on their different sensitivities to speech features, the auditory and visual systems produce partially independent and complementary linguistic representations that constrain linguistic inference by selectively removing linguistic competitors that aren't consistent with both inputs. This process has been resolved at the word level for audiovisual speech. However, there is neural evidence that a lexical selection process driven by acoustic speech updates with each incoming phoneme. Hypothesizing that vision impacts lexical inference at the phoneme level, we developed a model of lexical constraint that occurs phoneme-by-phoneme and is dependent on orthogonal auditory and visual representations of speech. This model predicts lexical activations for auditory and visual speech based on their phonological neighborhoods and audiovisual speech based on their intersection. We tested the model by e.g., quantifying its output's cohort entropy - a measure of the degree of lexical competition - on its ability to predict neural (EEG) responses in participants listening to audiovisual speech. Our preliminary evidence supports visual constraint of acoustic speech inference happens sublexically and updates dynamically. Additionally, audiovisual responses reflect lexical inference based on visual cues more so when speech is degraded. We interpret our findings in context of a theoretical framework supporting multiple levels of visual integration along the acoustic-linguistic hierarchy. Finally, we discuss how these levels of visual speech processing and their integration with acoustic cues might map to dissociable behavioral, perceptual, and cognitive goals.

Disclosures: A. Nidiffer: None. **D. Hernández-Gutiérrez:** None. **E.C. Lalor:** None.

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Topic: E.08. Multisensory Integration

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Title: Visual speech enhances phoneme selectivity in human superior temporal gyrus

Authors: *Y. LI[1], I. DEWITT[4], J. BRENNAN[2], V. S. WASADE[6], W. C. STACEY[3], D. BRANG[5];
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Abstract: Visual speech information, such as lipreading, facilitates spoken word recognition, but the neural mechanisms underlying audiovisual speech perception remain poorly understood. Some evidence suggests that visual cues disambiguate fine-grained articulatory features during early perceptual stages, whereas other findings indicate integration at more categorical, phoneme-level processing. To test which speech representations were modulated by visual input, we analyzed intracranial electroencephalography (iEEG) signals recorded from epilepsy patients (n=12) performing an audiovisual speech perception task. Participants heard spoken words presented in either audio-only, visual-only, or congruent audiovisual formats. Stimuli were carefully controlled, consisting of sixteen words constructed from four initial consonants (/b/, /g/, /m/, /n/) and four balanced rimes (the vowel and any following consonants). We examined event-related potentials (ERP) in the superior temporal gyrus (STG) and trained support vector machine (SVM) classifiers to decode word labels from neural activity at individual electrodes. Decoding accuracy and classifier confidence were analyzed to capture both discrete improvements in classification outcomes and graded changes in representational strength. Decoding performance was then hierarchically evaluated at the word, phonemic, and phonetic levels to determine the representations affected by visual speech. Congruent visual speech increased classifier confidence for phoneme representations and improved decoding accuracy at both the word and phoneme levels. In contrast, no audiovisual enhancement was observed for phonetic features. Time-resolved analyses further revealed earlier successful decoding in audiovisual relative to auditory-only conditions, with these benefits primarily observed for onset consonants rather than rime information. Together, these findings support a model in which visual speech sharpens categorical phoneme representations in human STG rather than enhancing lower-level phonetic features. Accelerated processing and improved word recognition may therefore emerge as downstream consequences of phoneme-level representational sharpening.

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Topic: E.08. Multisensory Integration

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Title: Phoneme overlap analysis of the visual benefit for speech-in-noise perception

Authors: *J. F. MAGNOTTI[1], Y. ZHANG[2], L. L. ZHU[3], Y. YU[4], M. BEAUCHAMP[1];
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[3]Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Seeing the face of the talker improves the intelligibility of speech-in-noise, termed the visual benefit. The visual benefit is usually measured at the whole-word level, with responses classified as "correct" or "incorrect". An alternative method measures visual benefit using the phoneme overlap between stimulus and response. In 55 participants presented with auditory and audiovisual words, phoneme-overlap analysis estimated 289 different visual benefit values, compared with only three different values for whole-word analysis. Phoneme-overlap detected a positive visual benefit in 67% of word-participant pairs, in contrast to 32% for whole-word analysis. Individual words varied greatly in their phoneme-overlap visual benefit, from 1% to 72%. Variability across words was accurately predicted ($r = 0.78$) by the phoneme composition of the word and the visual benefit for untested words could be predicted with a median error of 9%. Measuring the visual benefit for individual phonemes revealed similarly high variability (1% to 70%) with six phonemes (W, F, V, TH, P, AW) exhibiting visual benefit more than one standard deviation above the mean. The increased sensitivity of phoneme-overlap analysis relative to conventional whole-word analysis may provide a useful tool for investigating audiovisual speech perception in clinical, neuroscience and computer science contexts.

Disclosures: J.F. Magnotti: None. **Y. Zhang:** None. **L.L. Zhu:** None. **Y. Yu:** None. **M. Beauchamp:** None.

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Presentation Number: NANO18.07

Topic: E.08. Multisensory Integration

Support: 5R01NS065395-14

Title: Noisy audiovisual speech perception by humans and artificial neural networks

Authors: *H. MA, Z. WANG, X. ZHANG, J. F. MAGNOTTI, M. S. BEAUCHAMP;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Seeing the face of the talker helps humans understand speech in noisy environments. An artificial neural network (ANN) known as AVHuBERT (Audiovisual Hidden-unit Bidirectional Encoder Representations from Transformers) combines information from the face and voice of the talker to transcribe speech (Shi et al., 2022). We compared the perception of the same noisy speech stimuli by AVHuBERT and 55 human participants. The stimuli consisted of 111 different words recorded by 12 speakers (6 female speakers), presented in auditory-only

(Ao) or audiovisual (AV) formats. The auditory-only accuracy was subtracted from the audiovisual accuracy to calculate a measure of visual benefit for each word and phoneme.
For AVHuBERT, all phonemes showed a positive visual benefit, illustrating its ability to use visual information to compensate for degraded auditory input. In human observers, however, the visual benefit varies substantially across phonemes. Some phonemes are associated with distinctive mouth shapes (e.g. upper teeth contact the lower lip for "F" or "V"), while others involve less distinctive articulatory movements (e.g. relatively uniform open-mouth shapes for many vowel sounds).
Phonemes were ranked by visual benefit. The Spearman rank correlation between humans and AVHuBERT was high, $r = 0.57$ ($p = 0.0004$). In human observers, six phonemes showed a visual benefit more than one SD above the mean: W, F, V, TH, P, and AW. Of these, all except for "W" were in the top seven phonemes for AVHuBERT. Conversely, for AVHuBERT, the phonemes with the highest visual benefit were F, TH, B, P, M, V, and AW. Humans showed a high visual benefit for five of these phonemes (all except B and M).
A linear model based on the phoneme composition of words successfully predicted audiovisual benefit for entire words in AVHuBERT (median leave-one-out prediction error = 0.06), comparable to prediction accuracy of the same model fit to human data (error = 0.09).
These results demonstrate substantial similarity between humans and AVHuBERT in how visual speech influences the perception of noisy auditory speech. Recently, we showed that AVHuBERT reports the audiovisual speech illusion known as the McGurk effect (Ma et al., 2026, PMID: 41709058). Similarity to human perception across stimulus types suggest that ANNs such as AVHuBERT may serve as useful models for investigating the perceptual and neural mechanisms underlying audiovisual speech perception.

Disclosures: H. Ma: None. **Z. Wang:** None. **X. Zhang:** None. **J.F. Magnotti:** None. **M.S. Beauchamp:** None.

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Presentation Number: NANO18.08

Topic: E.08. Multisensory Integration

Title: Prestimulus large-scale directed connectivity patterns predispose multisensory perception

Authors: *V. SINGH[1], V. KUMAR[2], A. BANERJEE[1], D. ROY[3];
[1]Cognition & Computation, Natl. Brain Res. Ctr. (NBRC), Manesar, India; [2]Neurol., Penn State Col. of Med., Hershey, PA; [3]Cognitive Brain Dynamics and connectivity lab, Indian Inst. of Technol., Jodhpur, India

Abstract: Perception emerges from the dynamic interplay of large-scale functional networks that integrate sensory input with the brain’s internal state. Previous studies suggest that variability in perception arises from differences in the functional organisation of these cortical networks.

While prior research has identified specific brain regions during the McGurk illusion, how prestimulus dynamic whole-brain connectivity shapes this phenomenon at the single-trial level remains unclear. To address this, we employed an existing EEG dataset to investigate trial-wise prestimulus functional connectivity (FC) dynamics and their role in modulating illusory perception. We first analysed time-frequency-resolved (tf) global coherence in the sensor space to identify significant FC before illusion using a linear mixed-effects model. We then estimated cortical sources for these tf-windows and extracted source time-series from relevant regions of interest. Next, we applied pairwise conditional Granger causality (GC) to assess directional interactions between these regions, followed by logistic LASSO regression to identify the most predictive connections for illusory perception. Our results revealed lower global coherence in the late beta (-400ms to -50ms; 16 - 18 Hz) and whole gamma (-800ms to 0ms; 39-42 Hz) at the sensor level (Fig.1). Source-level GC analysis with LASSO regression revealed key frequency-specific directed interactions preceding illusion. We observed STG-to-prefrontal and motor-to-whole-brain beta connectivity and occipital-to-prefrontal and prefrontal-to-fusiform gyrus gamma connectivity. These findings suggest that temporal fluctuations in the prestimulus whole-brain FC, specifically beta-gamma directional influences, play a critical role in shaping the McGurk perception. Thereby providing new insights into the neural mechanisms underlying multisensory integration and the predictive architecture of perceptual processes.

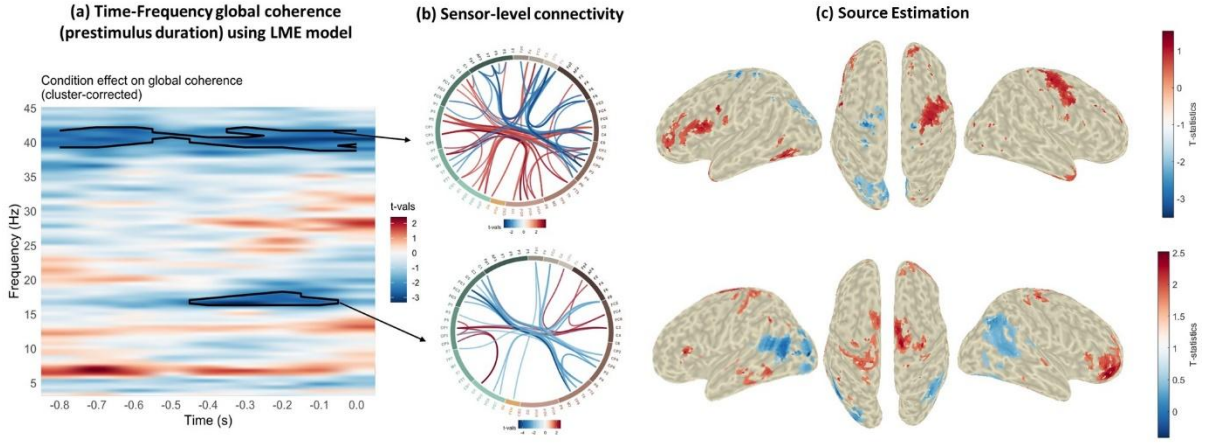


Fig.1: (a) Trial-wise time-frequency (TF) resolved global coherogram of the prestimulus duration ranging between -800ms to 0ms. The black contours indicate the significant clusters determined by cluster-based permutation testing on observed t-values (alpha = 0.05). (b) Sensor-level functional connectivity for the significant clusters TF-window. (c) Source power rendered over the cortical surface for gamma cluster (top) and beta cluster (bottom).

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Title: Selective exclusion of inactive neurons regulates ensemble plasticity

Authors: *S. D. EMERSON, T. CLARITY, R. BETHI, M. Z. LEONARD, K. THIBEAULT, E. S. CALIPARI;
Vanderbilt Univ., Nashville, TN

Abstract: Cocaine produces enduring behavioral changes by engaging small, transcriptionally active neuronal ensembles in the nucleus accumbens (NAc). These ensembles are essential for drug-associated learning, yet the molecular mechanisms that refine which neurons are recruited and re-recruited remain poorly understood. Here, we identify lysine acetyltransferase 2A (KAT2A) as an epigenetic brake underlying selective ensemble recruitment and re-recruitment. KAT2A was computationally predicted to regulate cocaine-induced gene expression in the NAc. Indeed, cocaine increased KAT2A recruitment to chromatin, and loss of function in D1 medium spiny neurons reduced cocaine locomotor sensitization and self-administration. However, single-nucleus RNA sequencing revealed that KAT2A was not enriched within transcriptionally active ensemble neurons; instead, its expression was highest in surrounding non-ensemble cells and was inversely correlated with immediate early gene induction. The negative association was strongest in NAc D1 medium spiny neurons. KAT2A loss of function enhanced cocaine-induced transcriptional activation, confirming its role as a negative regulator. With repeated cocaine exposure, KAT2A activity at chromatin increased in parallel with a progressive reduction in the number of transcriptionally active neurons. Longitudinal tracking of neuronal activity showed that, indeed, repeated exposure re-recruited a stable subset of hyperresponsive cells, and these neurons were defined by low KAT2A expression. Together, these results reveal that KAT2A functions outside ensembles to provide negative feedback that suppresses widespread transcriptional activation, thereby refining and stabilizing the core cocaine-responsive neuronal ensemble that drives drug-associated behavior. These data have broad implications for how neural epigenetic regulators contribute to the selection of the refined neuronal populations that drive behavior. Whether this exclusion-based mechanism generalizes beyond cocaine, and whether it can be exploited therapeutically to destabilize maladaptive ensembles, are open questions we are pursuing using activity-tagged single-cell sequencing.

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Nanosymposium

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Dopaminoceptive cells in the ventral hippocampus control cocaine action

Authors: *V. KONDEV[1], A. GODINO[2], B. T. KIPP[1], S. NAGUIB[4], A. LABANCA[5], T. MARKOVIC[6], E. KAHN[7], E. P. CHEN[1], C. BLASCHKE[1], M. ESTILL[1], L. GAN[8], P. ROUSSOS[3], E. J. NESTLER[9];
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Abstract: Dopamine signaling facilitates outcome valence, reward prediction error, and motivation; thus, dysfunctional dopamine signaling has been tied to several neuropsychiatric disorders, including substance use disorder (SUD) and depression. While most research has focused on striatal DA signaling, our lab and others have validated that the ventral hippocampus (vHPC) also exhibits topographical organization of mostly non-overlapping dopaminoceptive neuronal populations: those expressing the DA receptor type 1 (D1) or 2 (D2) (*Godino et al., Nature*). Here, we used fiber photometry, optogenetics, chemogenetics, and single nuclei RNA-sequencing (snRNA-seq) from D1- or D2-Cre mice to explore how dopaminoceptive cells in the vHPC control cocaine action. Male and female mice were exposed to cocaine conditioned place preference (CPP) or intravenous self-administration (IVSA). We reveal that vHPC D1 cell inhibition is necessary and sufficient for reward-context associations driving cocaine CPP and cue-induced reinstatement of drug seeking in self-administration models. On the other hand, vHPC D2 cell activation promotes positive reinforcement and chemogenetic modulation of these cells disrupts cue-induced cocaine seeking. snRNA-seq reveals potential molecular mechanisms, including endocannabinoid system elements, that might contribute to these effects. Together, these studies broaden our understanding of the role of DA within the larger mesocorticolimbic system and reveal new neuronal and circuit mechanisms underlying how drugs of abuse promote strong associative learning processes and facilitate drug seeking and taking characteristic of SUD.

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Title: H3K79 methyltransferase DOT1L gates cocaine-responsive transcriptional programs in D1 medium spiny neurons

Authors: *E. KIRCHNER[1], V. SUBRAMANIAM[2], E. J. NESTLER[2], P. MEWS[1];
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Abstract: Cocaine-responsive transcription in the nucleus accumbens (NAc) is central to reward-related plasticity, yet the chromatin regulators that shape these responses remain incompletely defined. Here, we identify DOT1L, a histone methyltransferase for histone H3 Lys79 (H3K79), as a mediator of cocaine-responsive molecular and behavioral adaptation in mice. Cocaine increased global H3K79 dimethylation (H3K79me2) abundance in the NAc and elevated *Dot1l* expression within a cocaine-responsive ensemble of D1 medium spiny neurons (MSNs) enriched for immediate-early genes. Pharmacological inhibition of DOT1L with pinometostat attenuated cocaine conditioned place preference and broadly attenuated cocaine-responsive transcriptional programs in the NAc, including pathways related to synaptic translation and chromatin regulation. Pinometostat-sensitive genes were preferentially enriched in the D1 MSN immediate-early-gene ensemble, consistent with elevated *Dot1l* expression in this population. In parallel, viral knockdown of DOT1L in D1 MSNs, but not D2 MSNs, reduced cocaine conditioned place preference, demonstrating cell-type-specific functional relevance. Finally, pinometostat-dampened gene programs were linked to transcriptional signatures observed in mouse NAc after cocaine self-administration and showed significant overlap with gene co-expression modules found in NAc of humans with cocaine use disorder. Together, these findings identify DOT1L as a regulator of cocaine-responsive transcriptional and behavioral plasticity in the NAc and support DOT1L inhibition as a candidate strategy to attenuate cocaine-associated molecular and behavioral adaptations.

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Presentation Number: NANO19.04

Topic: H.08. Drugs of Abuse and Addiction

Title: Spatiomolecular Organization and Cross-Region Transcriptional Coherence of Dopaminergic and Combinatorial Cell Types in the Human VTA

Authors: *B. A. OSTER[1,4], H. R. REUTER[4], S. VOGETY[4], N. EAGLES[4], S. V. BACH[4], S. E. MAGUIRE[4], M. MAYEN QUIROZ[4], K. D. MONTGOMERY[4,1], M. TIPPANI[4], J. KIM[4], R. A. MILLER[4], R. A. PHILLIPS, III[4], R. BHARADWAJ[4], J. MIRANDA-BARRIENTOS[4], J. E. KLEINMAN[4,2], T. M. HYDE[4,2,3], S. C. PAGE[4,2], L. COLLADO TORRES[4,5,6], K. R. MAYNARD[4,2,1];
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Abstract: The ventral tegmental area (VTA) and its mesolimbic dopamine (DA) projections to the nucleus accumbens (NAc) are dysregulated in neuropsychiatric disorders, including major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and substance use disorder (SUD). While single-cell and spatial transcriptomic approaches have revealed spatially organized VTA cell types in rodents, whether this organization is conserved in the human brain is poorly understood. To address this gap, we generated the first integrated single-nucleus RNA sequencing and spatial transcriptomic map of the postmortem human VTA using the 10x Genomics 3' gene expression and VisiumHD platforms across 10 neurotypical adult donors (5M/5F), profiling ~130K nuclei. Midbrain tissue sections were cryosectioned and subjected to RNAscope single molecule fluorescence *in-situ* hybridization for neuroanatomical validation. Following sequencing, data were processed with CellRanger/Spaceranger, batch-corrected with *Harmony*, and clustered using Leiden and *Banksy*, respectively. Cell types were annotated based on canonical marker gene expression from the literature and integrated across modalities using *spatialLIBD*. Our analyses reveal substantial molecular heterogeneity within the human VTA, including transcriptionally distinct DA subpopulations that spatially registered to VisiumHD domains organized along the medial-lateral axis. We identified combinatorial neurons co-expressing DA, GABAergic, and/or glutamatergic markers, including a rare triple co-expressing population. Cross-species comparisons revealed both conserved and divergent features of VTA spatiomolecular organization relative to rodents. To identify VTA cell types and spatial domains associated with neuropsychiatric disease, we used *MAGMA* to assess the overlap of cell type markers with genes associated with risk for MDD, PTSD, and SUDs as identified by genome wide association studies. Finally, transcriptional coherence analyses and multicellular program decomposition (*MOFACellulaR*) across matched donors revealed differential coupling between VTA DA subpopulations and NAc medium spiny neuron subtypes, nominating subpopulation-specific circuit vulnerabilities within the human mesolimbic pathway. Together, these findings advance our understanding of how molecularly distinct VTA populations and coherence with their NAc targets may confer differential vulnerability to neuropsychiatric disorders, including SUDs.

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Lundbeck Foundation R359-2020-2301

Title: Mapping of striatal PKA activity reveals dopamine-hypersensitive D1R-neurons associated with cocaine-induced ensemble formation

Authors: *A. KONOMI PILKATI[1], C.-F. BOWIN[2], H. BURM[3], S. D. EMERSON[4], H. ELAM[4], A. ABDEEN[3], L. PAGGI[3], S. JAGER[2], S. OVROM[2], M. Z. LEONARD[4], D. GOMEZ[4], A. T. SÖRENSEN[2], J.-F. PERRIER[2], E. S. CALIPARI[4], K. L. MADSEN[2], U. GETHER[2]; [1]Copenhagen Univ., Kobenhavn, Denmark; [2]Copenhagen Univ., Copenhagen, Denmark; [3]Univ. of Copenhagen, Copenhagen, Denmark; [4]Vanderbilt Univ., Nashville, TN

Abstract: D1Rs are classically described as low-affinity dopamine receptors, thought to respond primarily to phasic, micromolar dopamine, while D2Rs are considered high-affinity, responding to tonic, nanomolar levels. Accordingly, only a small ensemble of striatal neurons, mainly D1R-MSNs, becomes transcriptionally active (e.g., c-Fos+) in response to natural rewards or cocaine, playing a key role in encoding behavior. Here, we investigate the dopamine sensitivity of individual D1R-MSNs in relation to tonic and phasic dopamine signaling and cocaine exposure. Using the PKA sensor ExRai-AKAR2 in striatal cultures, acute slices, through live imaging, we find that D1R-MSNs exhibit heterogeneous dopamine responses, with some neurons responding to nanomolar concentrations. This hypersensitive phenotype is more prominent in the striatum, more pronounced in the ventral striatum. The hypersensitivity phenotype is observed for other neurotransmitters including acetylcholine, serotonin, adenosine, and GABA and individual responsiveness can fluctuate over time. Increasing D1R expression enhances dopamine sensitivity, excitability and cFos expression upon tonic-like dopamine stimulation, linking receptor levels to functional responses. To connect D1-MSN dopamine hypersensitivity to transcriptional activation *in vivo*, we performed analysis from published single-cell RNA-seq from cocaine-treated rats. This approach revealed a striking positive correlation between D1R levels and cFos induction in cocaine ensembles, further confirmed with RNAscope. Lastly, artificially manipulating D1R levels via sparse overexpression in D1-MSNs appears to affect cocaine-induced ensemble selection. Together, our findings reveal functional heterogeneity in dopamine sensitivity across D1R-MSNs, challenging the classical receptor affinity models, and suggest that D1R expression-driven hypersensitivity promotes transcriptional activation and thereby recruitment of neurons during reward processing into memory shaping ensembles.

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Nanosymposium

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Presentation Number: NANO19.06

Topic: H.08. Drugs of Abuse and Addiction

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NIH Grant F32MH139150
Lieber Institute for Brian Development

Title: Spatiomolecular characterization of DRD1-expressing islands in the human NAc

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Abstract: The nucleus accumbens (NAc) is a GABAergic basal forebrain structure that is dysregulated in a variety of neuropsychiatric diseases. Recent studies have used next generation sequencing technologies to understand molecular heterogeneity and spatial topography of NAc cell types in rodents and non-human primates. These studies identified a novel cell type with high expression of dopamine receptor D1 (DRD1) and mu-opioid receptor (OPRM1), topographically organized into clusters known as D1-islands. Additional work from our group has demonstrated that D1-islands are present in the human NAc and may differ across the anterior-posterior (AP) axis. However, no studies focused on the molecular characterization of D1-islands across the AP axis exists for the human brain. To study the molecular signature of D1-islands across the AP axis, we collected 22 NAc tissue sections ~500 microns apart from two postmortem human donors (1M/1F). spatial transcriptomics identified two populations of DRD1-expressing islands that exhibit distinct transcriptional profiles. These populations differ based on their expression of OPRM1, as well as genes that encode secreted proteins such as SEMA5B and SEMA3E. In addition to unique molecular signatures, these cell types differ based on their topography within dorsal-ventral, medial-lateral, and AP axes. Current efforts are focused on targeted profiling of D1-islands with Visium-HD, a subcellular resolution spatial transcriptomics technology that measures over 18,000 unique genes. Together, these data have identified two

transcriptionally distinct populations of D1-islands in the human brain that exhibit unique topography across the AP axis.

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Nanosymposium

NANO19: Neural and Molecular Mechanisms of Addictive Drugs

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Topic: H.08. Drugs of Abuse and Addiction

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CIHR Postdoctoral Fellowship

Title: Investigating the role of unique ventral pallidal populations in opioid use disorder

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Abstract: Opioid use disorder (OUD) is a chronic, relapsing condition that is marked by enduring neuroplastic changes. A hallmark of OUD is drug intake despite negative consequences; while most individuals will self-administer opioids and stop when a punishment is introduced (**punishment-sensitive; PS**), a subset will persist (**punishment-resistant; PR**). This along with the severe physical and affective symptoms induced by cessation of opioids renders abstinence difficult to achieve.
Therefore, elucidating these molecular changes is critical to identifying novel therapeutics to treat OUD. The ventral pallidum (VP) is a central node in the basal ganglia, and its activity is necessary for opioid seeking and relapse. Despite this, little is known about how opioids modulate plasticity in the VP, and how this may lead to persistent changes in opioid-seeking. We developed a high throughput homecage oxycodone (OXY) self-administration paradigm that enabled us to test the punishment sensitivity of mice by pairing OXY with a probabilistic air puff. Like human populations, we found that most mice stopped OXY intake (PS), which a subset continued (PR). We found that punishment sensitivity is dissociable from opioid re-seeking after withdrawal, which suggests multiple forms of behavioural plasticity converge in the VP. To this end, we molecularly profiled the VP and its projections and identified several opioid-sensitive neuronal populations. Amongst these was an inhibitory Bnc2-expressing cluster that projects to the VTA, which distinguishes PR from PS mice. These results suggest that

transcriptional remodelling of VP Bnc2+ neurons modulates VTA responses to reward, biasing mice towards more persistent seeking despite punishment. Consistent with multiple forms of opioid-induced behavioural plasticity, we also identified neuronal clusters implicated in withdrawal, which are distinct from the cluster involved in PR OXY consumption. Differential gene expression highlighted a vGlut2+ subpopulation as maximally affected by acute withdrawal. Through selective ablation, we determined that these neurons are essential to the development of withdrawal symptoms and OXY re-seeking after withdrawal. Given the previously described role of these cells in aversion, our results suggest that VP vGlut2 activity is increased during withdrawal, driving the aversive state that leads to maladaptive seeking and relapse.
Together, this work provides critical insight into the cellular heterogeneity of the VP and identifies several neuronal populations as important targets in treating maladaptive opioid seeking across multiple facets in OUD.

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Title: Exploiting cell type-specific epigenetic signatures for targeted functional manipulation of cocaine activated neuronal ensembles

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Abstract: Psychostimulant abuse poses a significant public health crisis and currently has no targeted intervention strategies. The orbitofrontal cortex (OFC) is involved in motivated and learned behavior and plays an important role in compulsive psychostimulant seeking and relapse. Cocaine induces chromatin and transcriptional reorganization within the OFC. These epigenetic modifications could sustain drug-seeking and other cocaine-driven maladaptations, but the

precise molecular and behavioral mechanisms that mediate these processes remain unclear. Single nuclei multiomic profiling was performed from OFC tissue taken from rats during a withdrawal period after cocaine intravenous self-administration to identify cocaine activated enhancers of interest. Multiomic profiling identified AP-1 motif enrichment at cocaine-activated enhancers within layer 4/5 intratelencephalic glutamatergic neurons of the OFC. Chemogenetic silencing of specific cocaine-activated enhancer tagged neurons within the OFC reduced cocaine seeking following withdrawal, suggesting that this ensemble regulates motivation for cocaine. In ongoing experiments, single nuclei multiomic profiling will be performed with OFC tissue taken from human samples who qualified for cocaine use disorder (CUD) compared to a control group. From this, we hope to uncover novel human-relevant enhancer targets for future experiments to better characterize enhancer function in CUD. The identification of cocaine activated enhancers may reveal key regions in the genome that facilitate molecular and behavioral responses to cocaine. Future intervention strategies could potentially target these sites to blunt cocaine seeking and subsequent maladaptations within the OFC.

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Accumbal cholinergic interneurons sustain maladaptive cue-driven motivation through an ISR-HCN2 axis

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Abstract: Cues paired with addictive drugs or highly palatable rewards can acquire excessive motivational power, but the cellular mechanisms that sustain maladaptive cue-driven motivation remain unclear. Here we identify nucleus accumbens cholinergic interneurons (CINs) as key regulators of this process. Drug and high-fat self-administration selectively increased CIN pacemaker firing, whereas sucrose self-administration did not. CIN ablation or bidirectional optogenetic manipulation respectively suppressed or enhanced cue-induced drug seeking. Drug experience engaged an integrated stress response in CINs, which upregulated HCN2 channels, increased I_h, and stabilized a hyperexcitable CIN state. CIN-specific HCN2 knockdown or HCN

blockade, including systemic treatment with the FDA-approved HCN blocker ivabradine, reduced cue-induced seeking across multiple addictive drugs and high-fat reward while sparing sucrose seeking. These findings define a cholinergic ISR-HCN2 mechanism that sustains maladaptive cue-driven motivation and provides a tractable target for relapse prevention

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Title: Protracted abstinence from methamphetamine self-administration results in exposure-dependent and cell-type specific changes in corticostriatal synaptic function

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Abstract: Illicit methamphetamine (meth) use continues to be problematic (UNODC, '25). Substance use disorders are postulated to involve progressive dorsal striatal engagement with a potential transition from the dorsomedial (DMS) to the dorsolateral striatum (DLS) with increasing disease severity (Lüscher et al., Nat Rev Neurosc, 247, '20). The DMS and DLS are primarily comprised of direct (dSPN) and indirect (iSPN) pathway spiny projection neurons that require excitatory input to drive action potentials. The orbitofrontal cortex (OFC) preferentially innervates the DMS and is implicated in goal-directed behaviors (Gremel et al., Nat Comm, 2264, '13), whereas the M1 motor cortex preferentially innervates the DLS and is implicated in habit (Hintiryan et al., Nat Neurosci, 1100, '16; Zhang et al., Sci Adv, 0854, '25). We hypothesized that abstinence from increasing levels of meth self-administration (MSA) would result in a progressive change in synaptic function first impacting OFC-DMS followed by M1-DLS SPNs. To test this, D1-TdTomato/D2-GFP mice self-administered meth (0.1mg/kg/infusion; fixed ratio 1 schedule) for 5 (2 hrs/day), 10 (2 hrs/day) or 14 (6 hrs/day) days; saline-yoked controls were run in parallel (4-6 mice/group; 3-4 iSPNs and/or dSPNs recorded/animal); AAV9-CamKII-chronos-eBFP was injected into the OFC or M1 1-4 days after the last operant session. After 21-24 days of abstinence, paired-pulse (PPR) and AMPA/NMDA (A/N) ratios were determined by whole-cell recordings with optogenetic stimulation. In male mice, there was no change in synaptic function after abstinence from 5 days, whereas abstinence from 10 days of MSA increased OFC-DMS dSPN PPR ($p<0.0001$), i.e. decreased glutamate release probability. This change normalized after abstinence from 14 days of MSA and M1-DLS dSPN A/N increased ($p=0.0125$). These data suggest a sequential OFC-DMS to M1-DLS change in synaptic function after abstinence from increasing levels of MSA in male mice. In contrast,

female mice showed increased OFC-DMS dSPN (p=0.0185) and iSPN (p=0.0190) PPR, OFC-DMS iSPN A/N (p=0.0047), and decreased M1-DLS dSPN A/N (p=0.0096) after abstinence from 10 days of MSA. After abstinence from 14 days of MSA, OFC-DMS changes and the decreased M1-DLS dSPN A/N normalized but M1-DLS dSPN PPR increased (p=0.0057). Altogether the presented data support sequential DMS-to-DLS changes in corticostriatal synaptic function exclusively in male mice after abstinence. In contrast, female mice show a broader pattern of impact, with changes in both DMS and DLS corticostriatal synaptic function after abstinence from 10 days that transition to DLS-only changes after abstinence from 14 days of MSA.

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Title: Single nucleus transcriptomic profiling of reward circuitry in a rat polysubstance drug-vs.-food choice model

Authors: *J. L. BELL[1], G. M. SILVA[5], X. QU[6], E. ALLEY[2], N. HESLEP[2], S. R. STRANDBERG[3], N. L. TRUBY[3], A. HASSAN[3], C. SMITH[3], R. K. KIM[3], J. A. PICONE[7], S. A. MARSH[8], J. LIU[4], M. BANKS[2], P. J. HAMILTON[3];
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Abstract: Among those diagnosed with substance use disorders (SUDs), there is high prevalence of polysubstance use, or the use of multiple substances either in combination or sequentially. Polysubstance use involving opioids such as fentanyl and stimulants such as methamphetamine represents a major and escalating public health crisis, and it is associated with elevated overdose risk, co-occurring psychiatric disorders, and poor treatment outcomes. However, the neurobiological mechanisms underlying vulnerability to drug choice over natural rewards remain

poorly understood. To address this gap, we combined a preclinical drug-vs.-food choice self-administration paradigm with single-nucleus RNA sequencing (snRNA-seq) to profile early transcriptional adaptations within the nucleus accumbens (NAc) and prefrontal cortex (PFC), two key regions regulating reward valuation and executive control. Male and female Sprague-Dawley rats were assigned to four cohorts 1) saline-, 2) fentanyl-, 3) methamphetamine-, or 4) combined fentanyl and methamphetamine(FM)- and could self-administer either 32% vanilla Ensure or drug during the choice procedure. In this choice procedure, we discovered a sex-specific vulnerability to polysubstance use as male, but not female, rats chose FM infusions at smaller unit doses than they did at single drug conditions. Following behavioral testing, 214,688 and 270,759 nuclei were isolated from the NAc and PFC for snRNA-seq, respectively. Clustering identified 26 transcriptionally distinct cell populations, including neuronal and glial cell types. Differential gene expression analysis and transposable element annotation were performed using cell type specific and pseudobulk approaches and generated against sex matched rats that underwent saline-vs.-food choice. Across conditions, we observed transcriptional adaptations within corticolimbic circuitry that varied by drug class and cell type, with neuronal populations particularly affected. Ongoing analyses are examining sex-dependent effects and convergent molecular pathways across fentanyl, methamphetamine or combined FM conditions. These findings provide a cell type-resolved molecular atlas of reward circuitry following drug-vs.-food choice and identify candidate transcriptional programs that may contribute to maladaptive decision making involved in heightened vulnerability to polysubstance use.

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Nanosymposium

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Topic: H.08. Drugs of Abuse and Addiction

Support: Rockefeller

Title: Low-Intensity Focused Ultrasound Rapidly Modulates Neuronal and Oligodendrocyte-Associated Signaling Networks in the Nucleus Accumbens

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Abstract: Low-intensity focused ultrasound (LIFU) is a non-invasive neuromodulation technology with emerging therapeutic potential for neurological and neuropsychiatric disorders.

Recently, LIFU targeting the nucleus accumbens (NAc), a key node of the brain reward circuitry, markedly reduced craving in patients with substance use disorder (SUD), with effects persisting for at least 90 days following treatment. However, the molecular mechanisms underlying these long-lasting therapeutic effects remain poorly understood. To investigate the acute molecular responses to LIFU, we performed proteomic and phosphoproteomic analyses of the NAc in C57BL/6J mice. Animals received a single LIFU treatment using a single-element ultrasound transducer optimized for mouse brain stimulation. NAc tissue was collected 10 min after stimulation and processed for total proteomic and phosphoproteomic analyses. Phosphopeptides were enriched using the High-Select TiO_2 Phosphopeptide Enrichment Kit prior to LC-MS/MS analysis. LIFU induced rapid molecular remodeling in the NAc. In the total proteomic dataset, 25.95% of detected proteins were significantly altered, including 15.15% upregulated and 10.80% downregulated proteins. In the phosphoproteomic dataset, 18.17% of detected proteins exhibited altered phosphorylation states, including 16.72% increased and 1.45% decreased phosphorylation. Notably, proteins decreased in both proteomic and phosphoproteomic datasets were enriched for oligodendrocyte- and myelination-associated markers, including Mobp, Mag, and Opalin, suggesting that LIFU also engages glial and white matter-related signaling mechanisms. In addition, proteomic analysis identified increased mRNA processing and decreased respiratory electron transport and mitochondrial pathways following LIFU treatment. Pathway analysis of phosphoproteomic data revealed enrichment of NMDA receptor signaling and postsynaptic events, indicating rapid modulation of neuronal signaling pathways. In contrast, SLC-mediated transmembrane transport and GPCR ligand-binding pathways were downregulated. These findings demonstrate that LIFU rapidly remodels both neuronal and oligodendrocyte-associated signaling networks within the NAc. The coordinated regulation of synaptic, myelination-related, and metabolic pathways suggests that LIFU may engage both neuronal and white matter mechanisms to modulate reward circuitry. These molecular signatures provide mechanistic insight into the therapeutic effects of LIFU in SUD, including alcohol use disorder.

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Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

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Title: Adaptive sparse factorization reveals condition-dependent neural ensembles across multi-trial recordings

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Abstract: Modern recording techniques capture large neural populations across many trials, where each trial is associated with multiple experimental variables such as stimulus identity, behavioral choice, and temporal context. A key challenge is to understand how these variables are encoded in population activity, and to disentangle the distinct contribution of each variable across trials. Standard population analyses either fit a single shared decomposition across all trials, which averages over cross-trial variability, or treat each trial independently, which discards the cross-trial structure. Neither approach can recover interpretable neural functional groups whose membership may shift across conditions. Here, we introduce a novel computational method that decomposes multi-trial population activity into sparse neural ensembles, each associated with a specific experimental variable. Unlike standard decompositions, each ensemble's neuronal membership can subtly reorganize across conditions, which allows it to reveal task signals that reshape with changing experimental demands. Each ensemble is also paired with a temporal trace that captures its within-trial dynamics and varies from trial to trial, separating how neural populations respond to stimuli from how they reorganize over time. The method takes multi-trial recordings and iteratively learns ensemble structure by maximizing data reconstruction while enforcing cross-condition similarity, constraining the amount of adjustment across trials, and updating temporal traces to capture within-trial dynamics. We first validated the method on simulated data with known ground-truth ensembles, where it recovered ensemble membership and temporal traces more accurately than standard tensor decompositions and related approaches. Next, we applied the method to lateral entorhinal cortex recordings from rats performing a context-dependent odor-place association task. LEC single neurons exhibited prominent temporal drift at multiple timescales, and conventional analyses captured spatial context but failed to decode odor identity. Our method separated trial-by-trial and session-level drift into distinct ensemble types, recovering odor signals in the temporal traces that were otherwise lost to drift.

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Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

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Title: Potential mechanisms of perceptual constancy despite representational drift

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Abstract: In a phenomenon termed representational drift (RD), patterns of neural activity that correlate with certain environmental and behavioral features can exhibit apparently task-irrelevant dynamics. RD does not obviously affect task performance, and the mechanism which maintains task performance despite RD is yet undetermined. Two candidate mechanisms suffice, given that task performance is determined by some readout function of the drifting representations. One such mechanism is that of an adaptive readout, which tracks the drifting representations and undergoes sufficient modification to stabilize outputs. For example, certain plasticity rules can approximately stabilize outputs (Rule & O'Leary, 2022). The alternative mechanism is that of a constant readout, which requires that RD be constrained such that outputs are stable. These constraints could be realized in the long-timescale dynamics of continual learning with noisy inputs (Qin et al. 2023), and constrained drift has been shown to increase the robustness of learned representations (Natrajan & Fitzgerald 2025). Here, we consider the consistency of these mechanisms against experimentally observed RD.

In a flexible mathematical model, we found that output-stabilizing readout adaptations almost surely exist, granted sufficient dimensionality. We verified this finding by simulating completely random drift and computing the necessary readout adaptations. Additionally, we show that reciprocal learning rules in the drift and output populations can stabilize outputs, indicating that the necessary adaptations are biologically plausible.

Further demonstrating biological plausibility, we computed the output-stabilizing readout adaptations for observed RD in mouse primary olfactory (piriform) cortex (Schoonover et al., 2021). In a linear classification assay, the simulated adaptive readout maintained stable classification accuracy across all timescales. As such, we identified an adaptive readout which could maintain task performance despite RD.

While an adaptive readout could thus explain maintained task performance despite RD in the piriform, we cannot preclude a constant readout. In particular, we derived a necessity criterion for the detection of constrained RD. This criterion relates the number of unobserved neurons to the number of input features, and realistic values for each of these quantities do not satisfy this criterion. Thus the detection of constrained RD is seemingly prohibited with current experimental capabilities.

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Nanosymposium

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Title: Random network structure stabilizes neural manifolds

Authors: *J.-B. EPPLER[1], S. GALELLA[2], G. C. MEL[1], A. ROXIN[1];
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Abstract: Representational drift, the ongoing change in neuronal activity even under stable behavioral conditions, has been observed across many cortical and subcortical brain regions (e.g. Rokni et al. (2007), Ziv et al. (2013), Aschauer et al. (2022)). Paradoxically, representational similarity (i.e. the similarity between population activity patterns evoked by different stimuli) remains stable over time despite this drift (e.g. Gallego et al. (2020), Noda et al. (2025)). How can this stable representational similarity co-exist with ongoing activity changes on the level of neuronal populations?
We address this using binary feedforward networks with random connectivity, combining simulations and analytical results. We show that random projections generically preserve the similarity structure of inputs in output space: output similarity is a monotonically increasing function of input similarity, independent of the specific network connectivity. This holds for any sufficiently random, high-dimensional network with output space large enough to represent input structure. Modeling drift as random synaptic rewiring, this input-similarity preservation directly implies that representational similarities remain stable, even though population activity vectors change substantially. This extends to Hebbian learning and recurrent architectures.
If connectivity shaped by learning from high-dimensional inputs behaves statistically like random projections, similar similarity-preserving properties should also emerge in trained deep neural networks (DNNs). Importantly, these networks are not random but acquire structured connectivity through learning from high-dimensional inputs. Here, we model drift by continuing training beyond performance saturation. Within each layer, this leads to changing activity while representational similarity is largely preserved. Interestingly, drift magnitude increases with layer depth, mirroring experimental observations of greater drift in higher order regions, e.g. hippocampus, compared to early sensory areas.
Together, our results suggest that similarity-preserving properties characteristic of random projections provide a useful effective description for the experimentally observed coexistence of activity drift and representational stability.

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Title: Representational drift as a result of implicit regularization

Authors: *A. RATZON[1], D. DERDIKMAN[2], O. BARAK[3];
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Abstract: Recent studies show that, even in constant environments, the tuning of single neurons changes over time in a variety of brain regions. This representational drift has been suggested to be a consequence of continuous learning under noise, but its properties are still not fully understood. To investigate the underlying mechanism, we trained an artificial network on a simplified navigational task. The network quickly reached a state of high performance, and many units exhibited spatial tuning. We then continued training the network and noticed that the activity became sparser with time. Initial learning was orders of magnitude faster than ensuing sparsification. This sparsification is consistent with recent results in machine learning, in which networks slowly move within their solution space until they reach a flat area of the loss function. We analyzed four datasets from different labs, all demonstrating that CA1 neurons become sparser and more spatially informative with exposure to the same environment. We conclude that learning is divided into three overlapping phases: (i) Fast familiarity with the environment; (ii) slow implicit regularization; and (iii) a steady state of null drift. The variability in drift dynamics opens the possibility of inferring learning algorithms from observations of drift statistics.

Disclosures: A. Ratzon: None. **D. Derdikman:** None. **O. Barak:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.05

Topic: I.08. Learning and Memory

Support: Max Planck Society

Title: Representational drift is insensitive to altered levels of inhibition

Authors: *U. LEWIN[1], J. BAUER[2], Y. ZHANG[1], T. BONHOEFFER[1], M. HUEBENER[1]; [1]Max Planck Inst. for Biol. Intelligence, Martinsried, Germany; [2]Sainsbury Wellcome Centre, UCL, London, United Kingdom

Abstract: Representational drift - the progressive decrease in the similarity of a neural representation across days to weeks under nominally constant conditions - challenges the intuitive assumption that stable perception requires a stable neural encoding of the world. Understanding which mechanisms constrain the nature and magnitude of drift will be necessary for explaining how drift arises, how it can be compared across circuits and modalities, and how it is used or compensated for by the brain to support stable behavior. The preferred orientation of neurons in mouse primary visual cortex is a well-suited model system for investigating the principles that govern stable feature representations. It offers both a detailed understanding of the underlying circuitry and shows moderate but reliable representational drift.

PV interneurons are strong candidates for regulating drift of orientation preference because they control different variables expected to determine tuning stability: pyramidal neuron activity, feature selectivity, population coactivation, and cortical plasticity. Reducing PV-mediated inhibition should therefore broaden tuning, increase shared activity among differently tuned neurons, and expand the range of orientations over which plasticity can alter excitatory responses. We therefore hypothesized that PV interneuron activity constrains representational drift by limiting tuning width and coactivation among excitatory neurons.

To test this, we chemogenetically reduced PV interneuron activity in the primary visual cortex of adult mice for one week, while performing daily two-photon calcium imaging. Sustained inhibition of PV interneurons increased pyramidal neuron activity, broadened tuning curves, and increased pairwise correlations for several days. To evaluate the effects of PV interneuron activity on representational drift, we then followed the orientation preference of the same neurons over many weeks, while inhibiting PV neurons for one of those weeks. Surprisingly, this substantial circuit-level perturbation of the excitatory-inhibitory balance not only had no effect on the magnitude of representational drift in preferred orientation but also left population-level metrics of drift unchanged. Moreover, the observed drift magnitude was indistinguishable from our previously reported findings.

Thus, while PV interneurons in primary visual cortex shape the activity and tuning of excitatory neurons, they do not govern long-term tuning stability. Given the central role of PV interneurons in cortical circuitry, these findings question a link between circuit-level activity patterns and representational drift.

Disclosures: U. Lewin: None. **J. Bauer:** None. **Y. Zhang:** None. **T. Bonhoeffer:** None. **M. Huebener:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.06

Topic: I.08. Learning and Memory

Support: ISF 1873/24

Title: Constraints and degrees of freedom of representational drift in entorhinal grid codes

Authors: *A. RUBIN[1], N. SADEH[1], Y. ZIV[2];
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Abstract: The hippocampus and entorhinal cortex are interconnected brain regions crucial for navigation and memory. Hippocampal place cells fire in specific positions within the environment (place fields), while entorhinal grid cells tile the environment using hexagonally arranged firing fields. The specific position of hippocampal place fields is thought to be inherited from the position of its upstream entorhinal grid fields, such that positional changes of entorhinal grid fields should result in positional changes to hippocampal place fields. While much work has been done to characterize how hippocampal representations of space change over weeks, the long-term dynamics of their upstream entorhinal grid codes have remained unexplored. Here, we longitudinally imaged hundreds of grid cells over weeks as mice repeatedly explore a familiar linear track and compared their spatial coding stability to that of hippocampal place cells. Entorhinal grid cells displayed substantial representational drift over days that was coherent within grid-module, reflecting changing anchoring to space. In contrast, hippocampal place cells showed non-coherent changes in their tuning and the collective spatial code remained anchored to the external reference frame. At the population-level, grid cells activity along the linear track corresponded to a slice through the 2D grid lattice. This slice maintained a stable orientation but shifted over days within that space, exposing a network mechanism that constrains changes in grid codes, and explaining our observations at the single-cell level. Together, these results provide the first description of long-term representational drift of entorhinal grid codes, and challenge current theories by demonstrating that hippocampal spatial representations can remain anchored in space despite substantial instability in their primary inputs.

Disclosures: A. Rubin: None. **N. Sadeh:** None. **Y. Ziv:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.07

Topic: I.08. Learning and Memory

Support: UIUC School of Molecular and Cellular Biology

Title: What do the different measurements of representational drift tell us?

Authors: *J. R. CLIMER[1], R. ENGELKEN[2], D. A. POSPISIL[3];
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Abstract: Across the brain neural tuning changes over days: neurons enter and leave the active representation and reshape their tuning. Measuring the properties of this "representational drift" precisely across brain regions, models, and contexts is essential for understanding how it shapes cognitive processes. But how is representational drift best measured? The systems neuroscience community has developed over twenty quantitative approaches, which can be grouped into single-cell metrics (e.g., tuning-curve correlation) and population-level metrics (e.g., population vector correlation). Because these measures rest on different assumptions and capture different features of change, this metric "zoo" makes comparisons across studies, brain regions, and species unreliable. We are simulating neural populations under experimentally motivated models with ground-truth parameters and quantify how faithfully each metric recovers the known drift. This lets us define what each metric actually measures, its sensitivity to factors unrelated to true drift (such as the number of recorded neurons, session duration, firing rate, and behavioral sampling), and its systematic biases. Together, these analyses will give the field a principled basis for selecting metrics, reconciling discrepant findings, and comparing observed drift to biophysical and normative models of the underlying circuits.

Disclosures: J.R. Climer: None. **R. Engelken:** None. **D.A. Pospisil:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

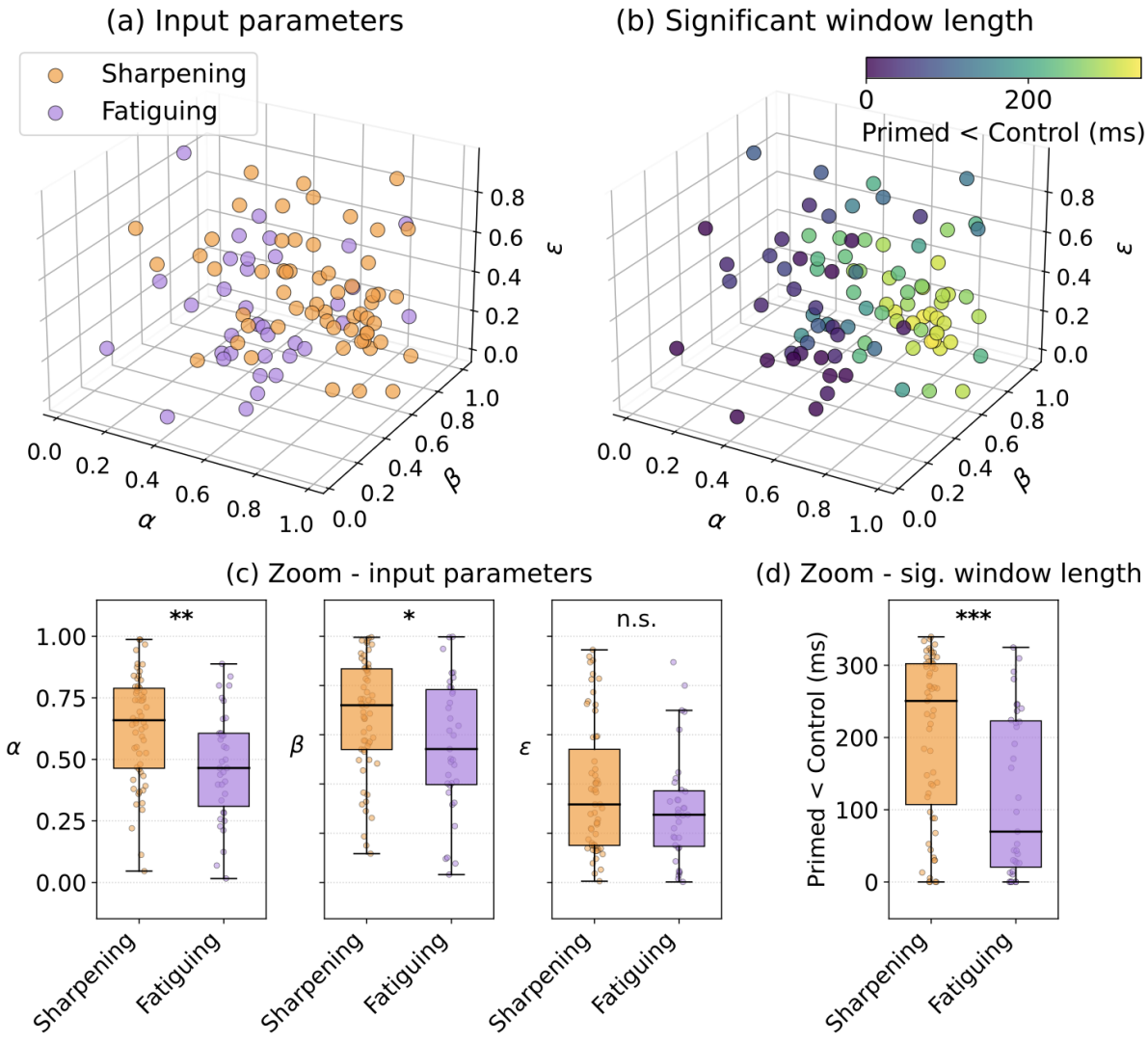
Presentation Number: NANO20.08

Topic: I.08. Learning and Memory

Title: Input Geometry Shapes Neural Adaptation: Sharpening and Fatiguing in a Recurrent Cortical Model

Authors: *D. BARTOLINI[1,2], T. P. REBER[3], T. TCHUMATCHENKO[4], M. VOIGT[2];
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Abstract: A key function of the human brain is its ability to dynamically adapt to novel contexts by integrating prior experience. While neural adaptation is widely observed across cortical systems, the microcircuit-level mechanisms governing its intensity and temporal dynamics remain unclear. To bridge this gap, we develop a recurrent network of AdEx neurons governed by a triplet STDP rule, designed to reproduce neural dynamics recorded via intracranial EEG from the medial temporal lobe of neurosurgical patients performing a visual semantic adaptation task. Using input organizations inspired by the experimental paradigm, we systematically vary input geometry to investigate its impact on adaptation dynamics. We find that neural adaptation emerges from recurrent dynamics shaped by learned connectivity, with both its magnitude and temporal profile depending on the geometry of the input space. This dependence gives rise, at the single-neuron level, to a continuum of response regimes ranging from sharpening-like to fatiguing-like dynamics. Sharpening-like responses dominate when inputs exhibit high within-category similarity and strong between-category separation, whereas fatiguing-like responses emerge under the opposite regime. Figure 1 quantifies this classification, linking stimulus geometry to adaptation dynamics in recurrent cortical-like circuits.Figure 1: Parameter-dependent classification of network behavior. Networks segregate into two classes based on input geometry. Legend: α: within-category similarity; β: between-category separation; ε: macro-category separation. Primed/Control: consecutive stimuli from same vs. different subcategory. (a) 3D scatter of networks in input parameter space. (b) Same networks color-coded by suppression window duration (ms). (c-d) Boxplots of input parameters and suppression duration by class. Asterisks: Mann-Whitney U test, two-sided; $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***); n.s., not significant.



Disclosures: D. Bartolini: None. **T.P. Reber:** None. **T. Tchumatchenko:** None. **M. Voigt:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.09

Topic: I.08. Learning and Memory

Support: NSF CRCNS

Title: Coupled Oscillator Modeling Reveals Hidden Spirals in Human Cortical Traveling Waves

Authors: *A. DAS[1,2], J. ZHANG[4], E. ZABEH[5], L. D. KOLIBIUS[1], U. R. MOHAN[6], G. ERMENTROUT[4], J. JACOBS[3];
[2]Neurol., [3]Dept. of Neurol., [1]Univ. of Chicago, Chicago, IL; [4]Univ. of Pittsburgh, Pittsburgh, PA; [5]Zuckerman Inst., Columbia Univ., NewYork, NY; [6]NINDS, NIH, Washington, DC

Abstract: Neural traveling waves are patterns of brain oscillations that propagate across the cortex to coordinate neural activity in space and time to support behavior. While traveling waves are often described as planar propagations across cortex, recent theoretical work predicts that more complex spatial patterns, including spiral dynamics, could organize large-scale neural computations but remain difficult to detect in the human brain. To investigate this, we analyzed electrocorticographic recordings from humans performing memory experiments. To characterize traveling wave patterns, we used independent component analysis, and showed that traveling waves propagated along the cortex in complex spatial patterns that correlated with behaviors such as memory encoding, maintenance, and retrieval. We then developed a novel computational framework based on coupled phase oscillators to model these wave patterns. Using this modeling, we found that planar waves (and certain other wave types such as concentric waves) originate from **frequency gradients where** faster oscillators lead slower ones, creating a continuous spatial phase lag that manifests as a planar wave moving across the cortex. In addition, this model also shows a strong basis for the existence for spiral/rotating waves (Ding & Ermentrout, 2022; Paullet & Ermentrout, 1994). However, in real experimental data, rotating waves such as spirals are observed less frequently than other wave types (Das et al., 2026) because they are superimposed on top of these other wave types such as planar or concentric waves. We applied coupled phase oscillator modeling on these complex spatial patterns of traveling waves, and identified new "hidden spirals" that were empirically invisible. The center of these hidden spirals shifted across the cortex to distinguish different behavioral states, such as memory encoding, maintenance, and retrieval. Together, these findings reveal that cortical traveling waves are governed by latent spiral attractor dynamics and suggest that rotating wave architectures provide a fundamental neurocomputational mechanism for flexible human memory processing.

Disclosures: A. Das: None. **J. Zhang:** None. **E. Zabeh:** None. **L.D. Kolibius:** None. **U.R. Mohan:** None. **G. Ermentrout:** None. **J. Jacobs:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.10

Topic: I.08. Learning and Memory

Support: NSF-GRFP
Yale Center for Clinical Investigation Junior Faculty Scholar Award (National Institutes of Health/NCATS KL2 TR001862 to E.V.G.)
National Institutes of Health (K01 AA027832 to E.V.G.)

Title: Cortisol dynamically changes cortical organization via intrinsic neural timescales with consequences for long-term memory

Authors: *A. R. WILLIAMS[1,2,3], B. HARRIS[6], R. F. HELFRICH[4,2,3,1], E. V. GOLDFARB[5,2,3,1];
[2]Interdepartmental Neurosci. Program, [3]Wu Tsai Inst., [4]Dept. of Psychology, [5]Psychiatry, [1]Yale Univ., New Haven, CT; [6]Psychiatry, UCLA, Los Angeles, CA

Abstract: Stress reshapes how the brain forms new memories, with well-characterized effects on hippocampal function but less understood consequences for cortex-wide processes that support information integration. Integration over time requires that neural populations hold information across extended windows, or timescales, operationalized as the lagged autocorrelation of a timeseries. These timescales are organized along a neurobiologically-defined sensorimotor-association (S-A) gradient that spans the entire neocortex. Although preliminary evidence suggests that timescales are sensitive to changes in brain state, it remains unclear if affective states such as stress reconfigure the timescale hierarchy and whether these changes are relevant to memory. Here, we replicate that timescales linearly increase along the S-A axis in fMRI (n=26), ECoG (n=20), and sEEG (n=20) datasets. To assess how timescales change under stress, we manipulated the cortisol component of the stress response in the fMRI dataset. Participants were given either 20 mg oral hydrocortisone or placebo pill in a cross-over double-blind experimental design. Due to literature that suggests stress can disrupt memory integration, we hypothesized that cortisol would shorten timescales specifically in association cortex. Contrary to our hypothesis, we found that, at rest, cortisol selectively lengthened timescales in sensory cortex, flattening the hierarchical gradient. To identify a candidate molecular substrate of this effect, we generated transcriptomic maps from post-mortem microarray gene-expression data (Allen Human Brain Atlas). Strikingly, glucocorticoid and other stress-relevant receptor genes were significantly enriched in sensory cortex (spin permutation corrected), overlapping with the regions that had lengthened timescales under cortisol. Finally, we offer evidence that these changes may be relevant for cognition by analyzing timescales during a long-term memory task. During memory encoding, timescales broadly decrease across all cortical regions. Ongoing analyses will probe the relationship between timescales across the hierarchy, cortisol levels, and later memory retrieval. Altogether, we present evidence that cortisol reorganizes where in the cortical hierarchy information is held over time, and that this reorganization tracks both receptor anatomy and future memory.

Disclosures: A.R. Williams: None. **B. Harris:** None. **R.F. Helfrich:** None. **E.V. Goldfarb:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.11

Topic: I.08. Learning and Memory

Title: Neural dynamics of past recall and future planning during navigation of abstract space

Authors: *Y. YANG, Q. YU;
Inst. of Neuroscience, Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sciences, Shanghai, China, Shanghai, China

Abstract: Mental travel to the past and future is thought to rely on overlapping neural systems, yet the mechanisms differentiating them remain elusive. We used magnetoencephalography (MEG) to investigate the neural dynamics of retrospective recall and prospective planning during an abstract navigation task. Human participants learned a graph-structured map comprising distinct states within an abstract space. During MEG recording, they were cued to either retrieve a past path or plan a future path over a subsequent delay period. Our results revealed dissociable spatiotemporal, oscillatory, and reactivation profiles for past recall and future planning. First, source reconstruction of event-related fields (ERFs) revealed an early bilateral activation during past recall, reflecting retrieval of stored representations. In contrast, future planning elicited a late right-lateralized activation, possibly coordinating the generation and control of prospective sequences from memory. Second, past recall was accompanied by stronger alpha/beta activity and early theta responses, implicating reactivation and stabilization of stored representations. Future planning showed sustained delay-period theta enhancement, suggesting higher executive control demand for prospective computation. Finally, temporally delayed linear modelling (TDLM) revealed rapid sequential reactivation of states for both past and future paths during the delay period. Specifically, past recall was characterized by short-lag forward and backward sequences, whereas future planning expressed similar short-lag bidirectional sequences but uniquely engaged an additional slower forward sequential reactivation. Importantly, only the strength of slow-forward sequence during future planning positively predicted task accuracy across participants. In addition, analysis of alternative, unchosen paths revealed fast-forward sequences during future planning but not past recall, indicating that planning may initially sample possible routes transiently, while slower forward sequences may preferentially support the construction of behaviorally relevant future trajectories. Together, these asymmetric neural dynamics reveal how the brain differentiates between past and future to flexibly support memory-guided and goal-directed behaviors.

Disclosures: Y. Yang: None. **Q. Yu:** None.

Nanosymposium

NANO20: Stability and Change in Neural Representations: From Drift Mechanisms to Human Circuit Dynamics

Location: WCC Rm 145

Time: Monday, November 16, 2026, 8:00 AM - 11:00 AM

Presentation Number: NANO20.12

Topic: I.08. Learning and Memory

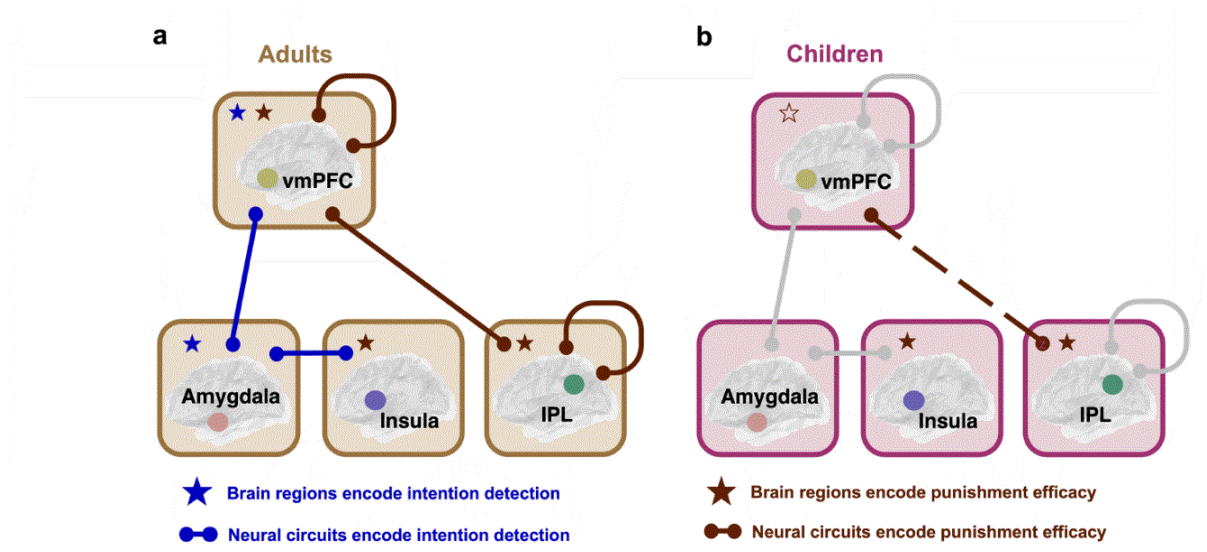
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MYRG of University of Macau, MYRG2022-00188- ICI

Title: Intracranial Insights into the Developing Neural Basis of Moral Punishment

Authors: *H. WU, K. HU;
Ctr. for Cognitive and Brain Sci. and Dept. of Psychology, Univ. of Macau, Macau, Macao

Abstract: Intracranial Insights into the Developing Neural Basis of Moral Punishment
Keyu Hu[1], Haoming Zhang[1], Jiayu Cheng[1], Yangchun Chen[2,3], Xiaobin Zhang[2,3], Changlin Bai[1], Fengpeng Wang[2,3], Yi Yao[2,3], Haiyan Wu[1*]
*1 Centre for Cognitive and Brain Sciences and Department of Psychology, University of Macau, Macau SAR, China 2 Epilepsy Center, Xiamen Humanity Hospital, Xiamen, China 3 Humanity Hospital-Shenzhen Institutes of Advanced Technology, Joint Center for Epilepsy Research, Xiamen, China * Corresponding author haiyanwu@um.edu.mo*
Third-party punishment (TPP) allows observers to sanction harm-doers even when they are not directly affected, requiring evaluation of harmful intention, emotion, and punishment efficacy. Yet how this capacity develops at the circuit level remains unclear. We recorded stereoelectroencephalography (SEEG) from 31 epilepsy patients, with 17 adults and 14 children, during a TPP task manipulating the attacker's intention and whether punishment outcomes met or violated expectations.
Behavioral modeling showed that adults incorporated both intention and prior punishment efficacy into decisions, whereas children showed more direct responses and weaker context-dependent adjustment. In adults, broad-band gamma activity in the amygdala and vmPFC differentiated inferred intention, and amygdala responses to intentional harm increased with age. Before later choices, IPL beta and broad-band gamma activity encoded prior efficacy, suggesting integration of outcome history into moral decisions. Connectivity analyses showed developmental refinement of task-relevant communication: adults showed intention-sensitive coupling among the amygdala, insula, and vmPFC, while IPL-vmPFC coupling and local synchronization within vmPFC and IPL strengthened with age when efficacy was salient. Task-resting similarity analyses further revealed age-dependent reconfiguration of amygdala-insula and IPL-vmPFC circuits.
Together, these intracranial findings indicate that mature moral punishment emerges through developmental refinement of subcortical-cortical circuits linking affective evaluation with cognitive integration, supporting a shift from intuitive punishment in childhood to more context-

sensitive decisions in adulthood.



Disclosures: H. Wu: None. **K. Hu:** None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.01

Topic: B.07. Network Interactions

Support: NIH R01NS105691
NIH R01NS115707
NSF CAREER CBET 1943906.
NIH NINDS T32 NS08674932
NIH BRAIN F32MH130022.

Title: Temporal modulation of cortical parvalbumin and somatostatin neurons shapes network activation and adaptation during microstimulation

Authors: *T. D. Y. KOZAI[1], **C. L. HUGHES**[2];
[2]Dept. of Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Parvalbumin-positive (PV) and somatostatin-positive (SOM) inhibitory interneurons play distinct and critical roles in shaping cortical sensory processing, yet their activation dynamics during patterned input remain unclear. Understanding how these interneurons respond to diverse temporal inputs is essential for both basic neuroscience and the development of effective neurostimulation strategies. We sought to gain deeper insight into the mechanisms by which PV and SOM interneurons regulate cortical activity during prolonged and patterned input

with clinically relevant stimulation patterns. We used two-photon calcium imaging in awake SOM-Cre and PV-Cre mice to record Layer 2/3 somatosensory cortex activity. Neurons were labeled with AAV-FLEX-tdTomato and calcium signals monitored via AAV-Syn-GCaMP7b. Microstimulation was applied at 10 and 20 μA using 11 stimulus patterns, including fixed frequencies (10-200 Hz), bursts (10 Hz burst, 20 Hz burst, theta burst), and dynamic (i.e., biomimetic) amplitude or frequency modulated patterns over 30 seconds.
Activation over time depended critically on the interaction between microstimulation amplitude, frequency, and duration. With high amplitude and high frequencies, both PV and SOM neurons were more strongly activated than unlabeled neurons. PV neurons exhibited greater stimulus-evoked adaptation than non-PV neurons. Low microstimulation frequencies and amplitudes only weakly recruited SOM neurons, implying more intense activation is required for SOM-mediated feedback. Burst patterns, especially those with higher intra-burst frequencies, evoked stronger and more sustained activation than fixed-frequency patterns, potentially by reducing SOM-related feedback. Theta-burst stimulation (TBS) more effectively activated PV neurons and facilitated SOM neurons across trials, indicating TBS can more strongly recruit inhibitory networks, providing a potential mechanistic basis for its therapeutic effects. Dynamic amplitude modulation effectively preserved excitatory-inhibitory balance by eliciting transient, consistent responses and avoiding long- term adaptation. These findings underscore the potential for amplitude-modulated stimulation to more closely mimic patterns of neural activation by maintaining excitatory-inhibitory balance.
This research has practical implications for optimizing microstimulation for sensory restoration and also provides insight into the circuit-level roles of PV and SOM neurons in regulating cortical dynamics, supporting ideas that these subtypes contribute to transient and sustained inhibitory control in cortical somatosensation.

Disclosures: T.D.Y. Kozai: None. **C.L. Hughes:** A. Employment/Salary (full or part-time):; Blackrock Neurotech.

Nanosymposium

NANO21: Network Interaction

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Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.02

Topic: B.07. Network Interactions

Support: NIH grant EY02874
NSF HDR Grant 2117997
Moorfields Eye Charity GR001264

Title: Inhibitory network predicts microstimulation-induced cortical plasticity

Authors: M. W. FANG[1], M. C. DADARLAT[3], ***Y. SUN**[2];
[1]Inst. of Ophthalmology, [2]Univ. Col. London, London, United Kingdom; [3]Biomed. Engin., Purdue Univ., West Lafayette, IN

Abstract: Intracortical microstimulation is a powerful tool for perturbing neural circuits, yet how circuits change post-stimulation remains poorly understood. Here, we combined chronic intracortical microstimulation with cell-type-specific two-photon calcium imaging to track excitatory and inhibitory neurons in layer 2/3 of the awake mouse primary visual cortex before, during, and after stimulation. Even after a short 15-min microstimulation period, robust and cell-type-specific changes were observed across four animals: excitatory neurons showed widespread suppression after stimulation, whereas inhibitory neurons showed enhanced activity, most prominently in neurons that were not recruited during stimulation. To identify circuit features that predict this reorganization, we quantified each neuron's post-stimulation change in activity and related it to recruitment during stimulation, local neighborhood structure, and pre-stimulation population coupling. Changes in excitatory neurons were best predicted by the recruitment pattern of nearby inhibitory neurons, indicating that local inhibitory engagement during stimulation constrains subsequent excitatory suppression. In contrast, changes in inhibitory neurons were better explained by pre-stimulation population coupling, suggesting that intrinsic network embedding determines how inhibitory neurons respond to perturbation. These results show that microstimulation-induced circuit reorganization depends strongly on inhibitory-network properties, an understudied factor that can be resolved with in vivo two-photon imaging. More broadly, our findings highlight how imaging-defined local circuit architecture, beyond stimulation-evoked responses alone, can improve the prediction of stimulation outcomes in cortical networks.

Disclosures: M.W. Fang: None. **M.C. Dadarlat:** None. **Y. Sun:** None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.03

Topic: B.07. Network Interactions

Support: NIH Grant K99EY034699

Title: Exciting excitation decorrelates visual cortical networks by recruiting inhibition, leading to improved perception.

Authors: *A. R. ANDREI[1], V. DRAGOI[2];
[1]Houston Methodist Res. Institute/ Rice University/ Weill Cornell Med., Houston, TX;
[2]Neurosurg., Methodist/Rice and Weill Cornell Med. Col., Houston, TX, TX

Abstract: Correlated activity represents a ubiquitous feature of neural responses in neocortex. The reduction in correlations, or "decorrelation", is generally believed to be a beneficial mechanism for stimulus coding and behavioral performance. Over the past several decades, neural network decorrelation has been observed across species during adaptation, attention, learning, and enhanced cognitive performance. However, despite its prominence, the beneficial

effects of decorrelation for neural function and behavior have not been demonstrated causally, as correlations are strongly linked with firing rates. Here, we describe a method to optogenetically reduce correlations while firing rates remain statistically unchanged. We transduced populations of excitatory neurons in primary visual cortex (V1) of two macaque monkeys with the gene for channelrhodopsin-2 (an excitatory opsin) under the α-CaMKII promoter. After several weeks, to allow for viral expression, electrophysiological recordings using multi-contact laminar arrays were conducted in conjunction with optogenetic stimulation. Monkeys performed a visual detection task to report the presence of oriented gratings of various contrasts. Visual stimuli were preceded by optogenetic stimulation (35 Hz, 10 pulses, 10 ms/pulse) on 50% of randomly interleaved trials. We found that optogenetic stimulation of populations of excitatory neurons are followed by a transient, but pronounced, reduction of correlations across the network (n=4733 pairs) up to 400ms after light offset, during which time firing rates are statistically indistinguishable between laser and control trials. We emulated our experimental design using a balanced computational model comprised of 8,000 excitatory (50% modulated on pseudo-light trials) and 2,000 inhibitory neurons. The model replicated our experimental findings and revealed that the network decorrelation coincides with an increase in inhibitory synaptic strength during and after light stimulation. Importantly, the behavioral consequence of these network changes is that visual stimuli presented during this decorrelated state are perceptually more visible and are associated with more accurate information extracted from population activity. These results demonstrate that exciting excitatory populations has a ripple effect throughout the network, recruiting inhibition and resulting in surprising changes in network correlation structures.

Disclosures: A.R. Andrei: None. **V. Dragoi:** None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.04

Topic: B.07. Network Interactions

Support: Chinese NSF

Title: Cortical neuronal calcium dynamics of pulsed infrared neural stimulation: effect of state

Authors: *A. W. ROE[1], P. FU[2], S. SHOHAM[3], W. XI[4];
[1]Translational Neurosci., NYU & Nathan Kline Inst., New York, NY; [2]Sch. of Med., Wuhan Univ. of Sci. and Technol., Wuhan, China; [3]Neuroscience, Opthalmology, NYU Grossman school of medicine, New York, NY; [4]Zhejiang Univ., ZIINT, Hangzhou, China

Abstract: Motivation: Pulsed infrared neural stimulation (INS, 1875nm peak of energy absorption by water) is a non-viral method developed to activate single submillimeter sites in the brain. When used in ultrahigh field fMRI, it reveals functionally specific brainwide columnar

networks comprising synaptically activated nodes. INS is safe and effective for use in human cortex and is useful for neural and behavioral neuromodulation in primates. To investigate the specific cellular effects of this method, we used calcium imaging in mice to compare stimulation effects in awake vs anesthetized state. **Methods**: In vivo 2-photon calcium imaging was used to study GCaMP6s-labelled excitatory and inhibitory neurons in awake mice and following induction of anesthesia. In each state, pulsed infrared neural stimulation (0.25msec pulse width, 200hz, 0.5 sec) was used at low (<0.5 J/cm^2) and high (>0.5 J/cm^2) intensities. Responses of individual neurons were compared in awake vs. anesthetized states. **Results**: In excitatory neurons in anesthetized state, positive-going, intensity-dependent responses were observed in response to each INS pulse train (Fu⋯Roe 2024 Neurophotonics). However, surprisingly, in the awake state, the INS stimulation produced, in the same individual neurons, negative-going responses. To examine this result, in anesthetized state, we applied $GABA_A$ blocker picrotoxin, resulting in awake-like increased baseline fluorescence of individual neurons, leading to negative INS-induced responses. Application of the $GABA_A$ agonist muscimol in awake state, resulted in an anesthetized-like decreased baseline level, leading to positive INS-induced responses. Results at low intensities (typically used in previous INS studies) were intensity-dependent in each state. However, those at high intensities were partially attributable to measurable direct fluoro-thermal effects. Correlation analysis of baseline levels showed that strong INS response correlates with low baseline level, suggesting a greater sensitivity. Effects on inhibitory neurons differed in that responses were negative in both awake and anesthetized states. **Conclusion**: The results at low INS intensity are consistent with a feedforward inhibition model of synaptic response which is dependent on state-related potential levels. Our work also introduces a new tool for directly measuring and decoupling the thermal effects of INS *in situ*. In sum, our findings confirm that INS robustly modulates cortical neurons, further establishing its efficacy, and point to distinct state-dependent effects, making INS a potentially versatile tool for neuroscience and clinical applications.

Disclosures: A.W. Roe: None. **P. Fu:** None. **S. Shoham:** None. **W. Xi:** None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.05

Topic: B.07. Network Interactions

Support: R01EY023756
U19NS107613

Title: Feature tuned cortical microcircuitry supports flexible sensory representations

Authors: *H. ADESNIK;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Using focal, two photon holographic optogenetic stimulation, I will demonstrate that functionally aligned ensembles of cortical excitatory neurons specifically recruit co-tuned somatostatin inhibitory neurons. For sparse stimulation, this leads to feature suppression, while for dense stimulation this leads to pattern completion. This work reconciles prior conflicting results and establishes that a single and precise excitatory/inhibitory circuit in the mouse visual cortex can mediate opposite computations depending on the size of the recruited ensemble.

Disclosures: H. Adesnik: None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.06

Topic: B.07. Network Interactions

Support: R35NS132213

Title: A Basal Ganglia Pathway for Persistent Motor Recovery

Authors: *A. H. GITTIS;
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Deep brain stimulation (DBS) is an effective treatment for Parkinson's disease (PD), but its therapeutic effects are generally restricted to the period of active stimulation. We recently developed a circuit-inspired DBS paradigm to drive cell-type specific neuromodulation in the external globus pallidus (GPe), inducing a long-lasting recovery of movement that extends for hours beyond stimulation in dopamine depleted mice. Currently, the efficacy of cell-type specific DBS is being evaluated in a clinical study of Parkinson' patients. However, the neural circuitry underlying these long-lasting therapeutic effects remains unknown, limiting the identification of optimal stimulation targets and biomarkers for translation. Here we show that persistent therapeutic effects are mediated by a basal ganglia pathway that converges on the medial substantia nigra pars reticulata (SNr). Engagement of this pathway through multiple upstream nodes reliably induces sustained behavioral recovery and long-lasting electrophysiological changes in dopamine depleted mice. These persistent therapeutic effects are distinct from the transient benefits produced by global suppression of basal ganglia output. Together, these findings show that acute and long-lasting therapeutic responses are mediated by parallel, functionally independent circuits, providing a mechanistic framework for next-generation neuromodulation strategies that promote sustained recovery in advanced PD and establish circuit-level principles for translating cell type-inspired stimulation approaches to the clinic.

Disclosures: A.H. Gittis: None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.07

Topic: B.07. Network Interactions

Support: NIH RF1 NS126144

Title: Low Intensity Focused Ultrasound Preferentially Activates Inhibitory Neurons in Macaque Thalamic VPL Nucleus

Authors: *P.-F. YANG[1,2], N. ZHENG[2], A. PHIPPS[2], J. KUSUNOSE[2], C. CASKEY[1,2], **L. M. CHEN**[1,2];
[1]Radiology and Radiological Sci., Vanderbilt Univ. Med. Ctr., Nashville, TN; [2]Inst. of Imaging Sci., Vanderbilt Univ., Nashville, TN

Abstract: Low-intensity Transcranial focused ultrasound (FUS), combined with functional MRI (fMRI) monitoring, offers a precise and noninvasive approach for causally perturbing and dissecting functional brain circuits in both animals and humans. Our previous studies demonstrated that FUS can elicit increases in BOLD fMRI signal amplitude, low-frequency local field potentials, and neuronal spiking activity within the ventroposterior lateral (VPL) nucleus of the macaque thalamus during the resting state. In the present study, we further characterized the firing properties of FUS-responsive neurons isolated from the VPL and classified them as putative excitatory and inhibitory neurons based on spike waveform duration (0.2 ms classification threshold) and firing rate (10 Hz cutoff threshold). To validate this classification approach, we used the spiking characteristics of excitatory neurons selectively activated by optogenetic stimulation as a ground-truth reference and compared them with neurons responsive to 8 Hz vibrotactile stimulation. To examine regional differences in the neuronal composition, we compared the proportion of excitatory neurons in the secondary somatosensory cortex (S2) and thalamic VPL.
Combining broad-spiking (BS) and narrow-spiking, low-firing-rate (NSL) neurons identified most optogenetically activated excitatory neurons, including 94.8% in VPL and 98.2% in S2. Optogenetic VPL neurons were 68.77% BS and 26.03% NSL, whereas S2 optogenetic neurons were 93.33% BS and 4.87% NSL. Using this BS+NSL criterion, 96.33% of FUS-responsive VPL neurons were classified as putative excitatory (including 31.19% BS, 65.14% NSL), and 3.67% putative inhibitory (narrow-spiking, high-firing-rate (NSH)) neurons. Tactile-responsive neurons were also mainly excitatory, with 93.60% (46.31% BS and 47.29% NSL) in VPL and 90.57% (74.06% BS and 16.51% NSL) in S2 classified as BS+NSL. Across all VPL neuron subtypes (BS, NSL, and NSH), optogenetic stimulation evoked spiking responses with shorter onset latencies and greater peak amplitudes than those elicited by FUS or tactile stimulation. Similarly, in S2, optogenetic stimulation produced faster and larger responses than tactile stimulation. Postmortem immunohistochemistry confirmed robust ChR2-mCherry expression in VPL and S2. In summary, FUS-responsive neurons were predominantly excitatory. Neurons responsive to tactile stimulation in both the thalamic VPL and S2 cortex were also primarily

excitatory. These findings demonstrate that optogenetic studies in nonhuman primates can provide a valuable ground-truth framework for neuronal classification.

Disclosures: P. Yang: None. **N. Zheng:** None. **A. Phipps:** None. **J. Kusunose:** None. **C. Caskey:** None. **L.M. Chen:** None.

Nanosymposium

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Presentation Number: NANO21.08

Topic: B.07. Network Interactions

Support: DARPA

Title: The Neural Basis of Direct Brain Stimulation: Open Questions and Animal Model Approaches

Authors: *J. JACOBS[1], U. R. MOHAN[2];
[1]Neurol., Univ. of Chicago, Chicago, IL; [2]NINDS, NIH, Washington, DC

Abstract: Direct electrical brain stimulation holds enormous therapeutic promise, with established applications in Parkinson's disease, epilepsy, and depression, and emerging potential in memory disorders and psychiatric disease more broadly. Yet despite decades of clinical use, we still lack a mechanistic understanding of how stimulation parameters translate into specific neuronal outcomes, a gap that severely limits our ability to design and optimize stimulation-based therapies.Our group recently conducted a large-scale study of direct brain stimulation in human neurosurgical patients, using concurrent intracranial recordings to map how different stimulation parameters modulate neuronal activity across the brain (Mohan et al., 2020). This work revealed fundamental organizational principles: low-frequency stimulation predominantly inhibits neuronal activity, high-frequency stimulation drives excitation, and electrode sites near white matter preferentially produce excitatory responses. Yet these patterns tell only part of the story. Response patterns varied substantially across stimulation sites within the same individual, and correlated responses across sites were observed in only ~16% of patients. What drives this variability, whether local cytoarchitecture, fiber tract organization, connectivity differences, or disease state, remains poorly understood and represents one of many open questions about how stimulation shapes brain activity.Answering these questions requires experimental tools that human recordings simply cannot provide. Animal models offer cell-type-specific resolution, direct circuit access, and precise experimental control, making them essential for translating the phenomenology of stimulation-induced activity changes into genuine mechanistic principles that can guide next-generation therapies.

Disclosures: J. Jacobs: None. **U.R. Mohan:** None.

Nanosymposium

NANO21: Network Interaction

Location: WCC Rm 144

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO21.09

Topic: J.08. Methods to Modulate Neural Activity

Support: Samsung Research America--New Digital Biomarkers and Interventions to Monitor and Improve Sleep and Mental Wellbeing

Title: Acute effects of perceptible and imperceptible gamma sensory stimulation

Authors: E. TUBBS, *N. WHITMORE, J. CHEN, M. MELIKA, P. MAES;
MIT, Cambridge, MA

Abstract: Gamma-frequency sensory stimulation has shown to protect against neurodegeneration in animal models when administered over weeks, but the acute effects of gamma stimulation on physiology and cognition remain poorly defined. To this goal, we evaluated the effect of sensory gamma stimulation on a broad range of cognitive, EEG, and cardiovascular metrics in healthy adults (N=40) while also examining the effect of stimulus modality (visual vs haptic), periodicity (periodic vs aperiodic stimulation) and stimulus perceptibility (perceptible vs imperceptible). Participants completed a within-subject experiment with six conditions: periodic visible flicker, periodic imperceptible flicker, aperiodic visible flicker, wrist haptic stimulation, auricular vagus stimulation, and no-stimulation control. . Periodic visual flicker significantly increased gamma power (pFDR=.0092); indivisible stimulation produced a similar but weaker effect. Effects on heart rate and skin conductance responses varied by stimulus type. We found no acute cognitive effects of stimulation; but increases in heart rate produced by visual stimulation correlated with poorer matrix reasoning performance (Wald X2(3)=10.87, p=.0124). Our results suggest that gamma stimulation does not modulate one process but rather produces multiple modality-specific and shared effects on brain dynamics and autonomic nervous function. Imperceptible or haptic stimulation may offer advantages over conventional visual stimulation.

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Nanosymposium

NANO21: Network Interaction

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Topic: J.08. Methods to Modulate Neural Activity

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DBT/Wellcome Trust Intermediate Fellowship (IA/I/22/1/506257)

Title: Frequency-specific transcranial alternating current stimulation (tACS) engages dissociable neuromodulator-interneuron pathways: A precision neuromodulation approach

Authors: *H. BHARDWAJ[1,2], A. KUMARASAMY[1], C. ADAIKKAN[1];
[1]Ctr. for Brain Research, Indian Inst. of Sci., Bangalore, India; [2]Manipal Acad. of Higher Educ. (MAHE), Manipal, Karnataka, India

Abstract: Neuropsychiatric and neurodegenerative disorders, including Alzheimer's disease (AD), mood disorders, and schizophrenia, impose a growing global burden. Transcranial electrical stimulation (tES) is an emerging, non-pharmacological intervention for cognitive decline; however, empirically driven tES paradigms yield variable outcomes, and the underlying neurochemical mechanisms remain poorly understood. This study investigates how tES modality and frequency shape neuromodulator signalling, interneuron dynamics and molecular pathways in the prefrontal cortex (PFC). Recombinant AAVs were used to express genetically encoded acetylcholine, serotonin, dopamine, norepinephrine, and glutamate fluorescent sensors to monitor neuromodulator dynamics in the mouse PFC during tES. Calcium sensor (jGCaMP) expressed selectively in parvalbumin (PV) interneurons was used to examine PV interneuron activity. Fiber photometry was performed in awake, freely moving mice during tES. Proteomics was performed after chronic-tES in the P301S tau mice. Theta-tACS (8 Hz) preferentially enhanced serotonergic signalling during the stimulation, whereas gamma-tACS (40 Hz) selectively recruited noradrenergic and cholinergic transmission, indicating frequency-specific effects. Glutamate levels increased in PFC across all modalities (anodal tDCS, theta-tACS and gamma-tACS), suggesting glutamate potentiation as a shared downstream mechanism of tES paradigms. Theta-tACS entrained PV interneuron activity without elevating overall firing. Gamma-tACS significantly increased PV interneuron activity, suggesting recruitment of fast-spiking inhibitory networks during stimulation in the PFC. Ingenuity pathway analysis from proteomics revealed serotonin receptor signalling as among the most significantly enriched biological pathways under theta-tACS relative to sham, while gamma-tACS preferentially modulated synaptic transmission pathways, most notably those associated with GABAergic signalling. These findings establish a frequency-neuromodulator coupling milieu linking various tES paradigms to defined neurochemical and circuit-level signatures. tACS frequencies produce specific effects leading to selective engagement of neuromodulator systems. These results will likely reframe how tES parameters should be chosen, and position tES for next-generation precision neuromodulation in AD and other neuropsychiatric diseases.

Disclosures: H. Bhardwaj: None. **A. Kumarasamy:** None. **C. Adaikkan:** None.

Nanosymposium

NANO22: Animal Models of Parkinson's Disease

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Topic: C.03. Parkinson's Disease

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Title: Primate-Specific PINK1 Expression and Parkin Phosphorylation are Key Determinants of Dopaminergic Neurodegeneration and α-Synuclein Pathology in Parkinson Disease

Authors: Y. WANG[1], X. XIONG[1], K. CHEN[1], Z. WANG[1], S.-H. LI[2], X. LI[3], ***W. YANG**[1]; [2]GHM Inst. of CNS Regeneration, [1]Jinan Univ., Guangzhou, China; [3]Human Genet., Jinan University, China, Guangzhou, China

Abstract: Mutations in PINK1 and Parkin cause early-onset Parkinson's disease (PD) through loss of function. Although extensive in vitro studies have shown that PINK1 phosphorylates and activates Parkin, in vivo evidence of PINK1-mediated Parkin phosphorylation in animal brains has been lacking, which has hindered our understanding of their functional roles in vivo. Methods: CRISPR/Cas9 was used to target PINK1 and Parkin genes, either in fertilized monkey eggs or in the brains of adult monkeys via stereotaxic injection of adeno-associated viruses (AAV). Neuropathological analyses and FDOPA PET/CT imaging were performed to assess dopaminergic neurodegeneration and monitor striatal dopamine release. Single-cell sequencing was used to characterize cellular alterations resulting from PINK1 or Parkin deficiency. Sucrose density gradient centrifugation was used to isolate subcellular organelle fractions from monkey brains. Results: (1) Using AAV-mediated CRISPR/Cas9 to knock down PINK1 or Parkin in the substantia nigra of adult monkeys (Macaca fascicularis), we successfully recapitulated both dopaminergic neuronal death and pathological α-synuclein aggregation. PINK1 deficiency caused more severe neuronal loss than Parkin deficiency in the monkey brain. (2) Parkin phosphorylation at Ser65 was strictly PINK1-dependent, and both proteins were selectively enriched in primate brains. (3) Interestingly, PINK1 expression was regulated at the protein level and depended on primate brain-specific proteolysis, generating a truncated PINK1-55 isoform that was selectively present in the primate brain. (4) Overexpression of wild-type Parkin, but not the phospho-deficient mutant S65A (which cannot be phosphorylated by PINK1), ameliorated neurodegeneration and α-synuclein pathology induced by PINK1 deficiency. Conclusion: Our studies in non-human primates provide the first in vivo evidence of PINK1-mediated Parkin phosphorylation in the brain and suggest that this phosphorylation event could serve as a therapeutic target for Parkinson's disease.

Disclosures: Y. wang: None. **X. Xiong:** None. **K. Chen:** None. **Z. wang:** None. **S. Li:** None. **X. Li:** None. **W. Yang:** None.

Nanosymposium

NANO22: Animal Models of Parkinson's Disease

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Presentation Number: NANO22.02

Topic:

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CIRM

Title: Engineering progranulin-enhanced human microglia for Parkinson's Disease Therapy

Authors: *S. NAGUIB[1], L. FAN[3], S. KIM[6], P. YE[4], Y. FENG[3], D. RITTER[8], M. MAHONEY[3], S.-I. LEE[3], E. S. TORRES[3], T. RAAD[3], G. PATWARDHAN[3], H. DAVTYAN[9], J. CHADAREVIAN[9], S. C. SINHA[2], M. BLURTON-JONES[10], T. M. DAWSON[7], L. GAN[5]; [2]Helen & Robert Appel Alzheimer's Dis. Res. Inst., [1]Weill Cornell Med. Col., New York, NY; [3]Weill Cornell Med., New York, NY; [4]Weill Cornell Med., Little Neck, NY; [5]Brain and Mind Res. Inst., Weill Cornell Med., New York, NY; [7]Inst. for Cell Engin., [6]Johns Hopkins Univ. Inst. for Cell Engin., Baltimore, MD; [8]Dup15q Alliance, New York, NY; [10]Neurobio. & Behavior, [9]Univ. of California, Irvine, Irvine, CA

Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative disorder, with approximately 60,000 new diagnoses annually. PD is characterized by progressive loss of nigrostriatal dopaminergic neurons and the pathological accumulation of alpha-synuclein (a-syn). Microglia, the brain's resident immune cells, are critical for maintaining homeostasis and responding to cellular stress, and their activation is observed across neurodegenerative diseases, including PD. However, whether activated microglia exacerbate or mitigate disease progression remains unclear.To address this, we generated human microglia overexpressing progranulin (PGRN-OE), a secreted protein implicated in multiple neurodegenerative disorders, including PD, and evaluated their therapeutic potential. Immunodeficient mice received bilateral striatal injections of a-syn preformed fibrils (mPFFs). One month later, following depletion of endogenous microglia, mice were engrafted with either wildtype (WT) or PGRN-OE human microglia in the hippocampus and cortex. Motor performance was assessed 4.5 months post-injection.Mice receiving PGRN-OE microglia exhibited significant improvements in rotarod performance compared to WT controls. Single-nuclei RNA sequencing revealed that PGRN-OE microglia dampen interferon-related gene expression. Conditioned media from PGRN-OE microglia was significantly less toxic to dopaminergic neurons than media from WT microglia,

correlating with reduced secretion of SPP1, a disease-associated microglial (DAM) gene. Inhibition of SPP1 alone phenocopied the neuroprotective effects of PGRN-OE microglia. Additionally, PGRN-OE microglia reprogram lipid metabolism in mPFF-injected mice, with ACSL4, a key ferroptosis regulator, central to these changes. Pharmacological inhibition of ACSL4 in dopaminergic neurons reduced cell death, mimicking the effect of PGRN-OE conditioned media.Critically, PGRN-targeted microglial replacement therapy protected against dopaminergic neuron loss compared to WT microglia. These findings demonstrate that PGRN overexpression reprograms microglial function, modulating inflammatory and lipid pathways, and offers a promising strategy for mitigating neurodegeneration in PD.

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Nanosymposium

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Topic: C.03. Parkinson’s Disease

Support: NIH R21AG085144
NIH T35AG044303
NIH R21AG064596

Title: Integrated Gait and Pose Analysis Utilizing Computer Vision for Parkinsonian Behavioral Phenotyping in Mice

Authors: *M. J. JENNINGS, A. ANIGBO, S. LIN, M. YANG, S. E. PRZEDBORSKI; Columbia Univ., New York, NY

Abstract: Synucleinopathies can be biologically advanced before overt parkinsonism is clinically apparent, highlighting the need for objective, sensitive motor endpoints. We examined the mThy1-α-synuclein line 61 (L61-Tg) mouse, which shows progressive synucleinopathy with early circuit dysfunction, using an integrated pipeline combining CatWalk XT gait analysis and markerless pose estimation from the same CatWalk videos. Male L61-Tg and nontransgenic littermates were assessed at 12 and 18 months. DeepLabCut tracking of four landmarks showed highest accuracy at the tail base. We thus quantified mediolateral instability as within-run variance of tail-base lateral position. L61-Tg mice exhibited increased tail-base lateral variance at both ages. CatWalk mixed-effects modeling identified six genotype-dependent parameters at 12 months, and a progressive increase in hind base of support at 18 months. Comparison across measures showed that discrimination between L61-Tg and non-transgenic was similarly high for hind base of support and tail-base lateral instability the two were nonetheless synergistic, and the

approaches are therefore complementary to one-another in the determination of synucleinopathy motor phenotypes. This combined gait-pose strategy provides scalable, interpretable endpoints for preclinical Parkinson-like phenotyping and therapeutic testing.

Disclosures: M.J. Jennings: None. **A. Anigbo:** None. **S. Lin:** None. **M. Yang:** None. **S.E. Przedborski:** None.

Nanosymposium

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Time: Monday, November 16, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO22.04

Topic: C.03. Parkinson's Disease

Title: Paradoxical dopaminergic responses in VMAT2 related parkinsonism-dystonia longitudinal human and mouse model study

Authors: *R. ALKHATER[1,2], N. STEINER[3], F. BEN-RACHED[5], H. FIUMELLI[4], P. J. MAGISTRETTI[6];
[1]KAUST Jhah, THUWAL, Saudi Arabia; [2]Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia; [4]Biol. and Envrn. Sci. & Engin. Div., [3]KAUST, Thuwal, Saudi Arabia; [5]King Abdullah Univ. of Sci. and Technol., thuwal, Saudi Arabia; [6]BESE, King Abdullah Univ. of Sci. and Technol., Thuwal, Saudi Arabia

Abstract: Paradoxical dopaminergic responses in VMAT2-related parkinsonism–dystonia: longitudinal human and mouse model study
Reem Alkhater[1,2,3], Nadia Steiner[2], Fathia Ben-Rached[2], Hubert Fiumelli[2], Pierre J. Magistretti[21]
Johns Hopkins Aramco Healthcare, Dhahran, Kingdom of Saudi Arabia
[2] King Abdullah University of Science and Technology, Thuwal, Kingdom of Saudi Arabia.
[3] Johns Hopkins School of medicine, Baltimore, Unite Status of America
Abstract
Background
Current therapies for Parkinson's disease (PD) target dopamine deficiency but are limited by dopamine hypersensitivity, and behavioral complications. These limitations are also evident in rare, early-onset genetic forms of parkinsonism, which may reveal adaptive mechanisms relevant to idiopathic PD. Parkinsonism-Dystonia Type 2 (PKDYS2), caused by biallelic mutations in *SLC18A2* encoding vesicular monoamine transporter 2 (VMAT2), is characterized by infantile-onset parkinsonism, dystonia, and a paradoxical response to dopaminergic treatment. The mechanism underlying this response remains unclear.
MethodsWe performed long-term clinical follow-up of 12 patients with PKDYS2 and generated a knock-in mouse model carrying a pathogenic *Slc18a2* variant identified in patients. Motor, and gait phenotypes were assessed longitudinally in mice, and transcriptomic analyses were conducted in the striatum and prefrontal cortex.
ResultsIn patients, levodopa monotherapy resulted in severe worsening of motor symptoms. In

contrast, pramipexole produced marked clinical improvement. Subsequent introduction of levodopa led to additional and sustained improvements in motor symptoms, with significant reductions in disability scores, particularly when treatment was initiated early. VMAT2 deficient mice recapitulated key clinical features, including dystonia, reduced locomotion, and impaired motor coordination. Transcriptomic profiling revealed region specific gene regulation, implicating altered dopaminergic responsiveness and maladaptive synaptic plasticity. **Conclusion**VMAT2 deficiency produces a state of functional dopaminergic failure accompanied by postsynaptic adaptation, providing a mechanistic explanation for dopamine hypersensitivity and paradoxical therapeutic responses in PKDYS2. These findings suggest that restoring network homeostasis through modulation of transcriptional regulators may complement dopamine replacement and inform new therapeutic strategies for PKDYS2 and for broader forms of PD.

Disclosures: R. Alkhater: None. **N. Steiner:** None. **F. Ben-Rached:** None. **H. Fiumelli:** None. **P.J. Magistretti:** None.

Nanosymposium

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Topic:

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UGA startup

Title: The Human LRRK2-R1441G Mutation Drives Age-Dependent Oxidative Stress and Mitochondrial Dysfunction in Dopaminergic Neurons

Authors: *H. ZHANG;
Col. of Vet. Medicine, UGA, Athens, GA

Abstract: Background: Mitochondrial dysfunction and oxidative stress are central to the pathogenesis of Parkinson’s disease (PD), particularly affecting substantia nigra pars compacta (SNc) dopamine (DA) neurons. Here, we investigate how the R1441G mutation in leucine-rich repeat kinase 2 (LRRK2), a key genetic contributor to familial and sporadic PD, impacts mitochondrial function in midbrain DA neurons. **Methods**: We employed a BAC transgenic mouse model overexpressing human LRRK2-R1441G (BAC-hR1441G) and crossed it with TH-mito-roGFP mice to enable mitochondria-targeted redox imaging specifically in DA neurons. Acute midbrain slices from 3-, 6-, and 10-month-old mice were imaged using two-photon microscopy to assess mitochondrial oxidative stress. In parallel, mitochondrial respiratory function, membrane potential flickering events, and expression of uncoupling proteins (UCP4/UCP5) were analyzed. Spatial transcriptomic profiling was performed using the

GeoMx® Digital Spatial Profiler to uncover associated molecular alterations. **Results:** We observed a progressive increase in mitochondrial oxidative stress in SNc DA neurons of BAC-hR1441G mice at 3, 6, and 10 months of age. This was accompanied by reduced respiratory complex activity, attenuated mitochondrial membrane potential flickering, and diminished expression of UCP4 and UCP5. Spatial transcriptomic analysis revealed dysregulation of genes linked to mitochondrial uncoupling, calcium signaling, and redox regulation in BAC-hR1441G SNc DA neurons. **Conclusions:** These findings reveal an age-dependent progression of mitochondrial dysfunction in BAC-hR1441G SNc DA neurons. Dysregulation of calcium channels and uncoupling proteins emerges as a key mechanism contributing to bioenergetic failure, suggesting potential therapeutic targets to mitigate PD progression.

Disclosures: H. Zhang: None.

Nanosymposium

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Topic: C.03. Parkinson’s Disease

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Title: Neuroanatomical and functional characterization of the respiratory impairments observed in a genetic model of Parkinson’s disease

Authors: *Y. C. AQUINO[1], L. M. OLIVEIRA, Sr.[3], M. OLIVEIRA[2], T. MACEDO[4], J. RAMIREZ[5], T. S. MOREIRA[1], A. T. TAKAKURA[6];
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Abstract: Parkinson’s disease (PD) is a disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra (SN). Patients with PD usually present classical motor symptoms, such as tremors, but they may also exhibit respiratory disturbances, which remain underexplored despite being a leading cause of mortality in this population. While respiratory dysfunction has been predominantly investigated in toxin-induced models, genetic models provide an important complementary approach due to their progressive nature. However, respiratory alterations in genetic models of PD remain poorly understood. We aimed to evaluate potential respiratory disorders throughout disease progression in a genetic PD model. To this end, animals generated by crossing DAT-IRES-cre$^{(+/+)}$ and Tfam$^{fl/fl}$ lines were used as the PD model. Whole-body plethysmography was used for functional analysis, the FlexiVent system for respiratory mechanics assessment, and immunohistochemistry to quantify neurons in the SN and assess potential neurodegeneration in respiratory nuclei in both PD model and control animals

(CEUA 3325170822). The PD model showed a 38.4% ($p = 0.0014$) loss of dopaminergic neurons in the SN. Regarding respiratory function at baseline, PD animals showed a 16.1% ($p < 0.0001$) decrease in respiratory frequency, a 28.2% ($p < 0.0001$) reduction in estimated tidal volume, and 39.7% ($p < 0.0001$) reduction in estimated minute ventilation. The mice also exhibited ventilatory dysfunction in response to hypercapnia and hypoxia. Conversely, respiratory mechanics parameters were preserved. Neuroanatomical analysis revealed a 29% ($p < 0.0001$) reduction in neurokinin-1 receptor density in the pre-Bötzinger complex (preBötC), 10.6% ($p = 0.0003$) in Bötzinger complex (BötC), and 8% ($p = 0.0032$) in rostral ventrolateral respiratory group in PD animals. Furthermore, decreases of 47.5% ($p < 0.0001$) and 10.3% ($p = 0.049$) in the number of phox2b^{+} neurons were observed in retrotrapezoid nucleus (RTN) and nucleus of the solitary tract, respectively. There was also a 13% ($p = 0.0156$) reduction in catecholaminergic neurons in the Locus Coeruleus, whereas no changes were observed in the raphe nuclei. Refined temporal analysis demonstrated that functional and neuroanatomical respiratory changes begin around day 108 of life, initially characterized by a reduction in baseline respiratory frequency associated with preBötC degeneration, followed later by involvement of the BötC and RTN. Therefore, this genetic PD model exhibits neuroanatomical and functional respiratory impairments, suggesting the involvement of central mechanisms in the breathing disorders in PD.

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Nanosymposium

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Location: WCC Rm 146C

Time: Monday, November 16, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO22.07

Topic:

Support: Fapesp
CNPq

Title: Selective optogenetic stimulation of the vagus nerve prevents breathing impairments observed in the 6-OHDA model of Parkinson’s Disease

Authors: *L. M. C. CABRAL[1], T. S. MOREIRA[2], A. T. TAKAKURA[3];
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Abstract: Neuroinflammation contributes to degeneration of brainstem respiratory nuclei and the development of respiratory dysfunction in Parkinson’s disease (PD). Vagus nerve stimulation (VNS), a therapeutic approach currently used for neuropsychiatric disorders, such as depression and anxiety, has emerged as a promising strategy to modulate inflammatory pathways. The 6-

hydroxydopamine (6-OHDA) model of PD reproduces respiratory déficits associated with brainstem neuroinflammation, providing a useful model to investigate therapeutic interventions. Here, we evaluated whether selective optogenetic stimulation of motor or sensory vagal fibers could attenuate neuroinflammation and prevent respiratory impairment in this model. Male and female Chat-Cre Ai32 and Vglut2-Ai32 mice received bilateral intrastriatal injections of 6-OHDA (10 µg/µL). Five days later, selective optogenetic stimulation of motor or sensory vagal fibers was performed (5Hz, 10 min). Respiratory activity by diaphragmatic electromyography was assessed five days after stimulation, followed by immunohistochemical analyses of brainstem respiratory regions. Optogenetic stimulation of either motor or sensory vagal fibers prevented the reduction in respiratory frequency induced by 6-OHDA lesions ($p=0.0004$ and $p=0.0182$, respectively). Both stimulation protocols also attenuated neuronal degeneration in the preBötzinger complex (preBötC) ($p<0.0001$ and $p=0.0128$, respectively) and retrotrapezoid nucleus (RTN) ($p<0.0001$ and $p=0.0206$, respectively), two key brainstem respiratory centers. Astrocytic labeling revealed pathway-specific anti-inflammatory effects, with motor vagal stimulation reducing astrogliosis in the RTN ($p=0.0234$), whereas sensory vagal stimulation reduced astrogliosis in the preBötC ($p=0.0072$). Together, these findings demonstrate that selective activation of distinct vagal pathways protects effects against respiratory dysfunction and brainstem neurodegeneration in the 6-OHDA model of PD, supporting vagal circuits as potential therapeutic targets for PD-related respiratory impairment.

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Nanosymposium

NANO22: Animal Models of Parkinson's Disease

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Presentation Number: NANO22.08

Topic: C.03. Parkinson’s Disease

Support: FAPESP 2025/11386-4

Title: Sex-dependent effects of aging on respiratory dysfunction in Parkinson's disease

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Abstract: Parkinson’s disease (PD) is associated with respiratory dysfunction, an important contributor to morbidity and mortality in affected patients. Although aging is the main risk factor for PD, the interaction between aging, biological sex, and PD-related respiratory impairment remains poorly understood. Here, we investigated whether aging differentially affects respiratory dysfunction and brainstem respiratory networks in male and females subjected to a bilateral intrastriatal 6-hydroxydopamine (6-OHDA) model of PD. Adult (3 months old) and aged (18

months old) male and female rats received bilateral intrastriatal injections of 6-OHDA or vehicle (CEUA:4476210224). Respiratory parameters were evaluated by whole-body plethysmography, pulmonary mechanics were independently assessed, and immunohistochemical analyses were performed in key respiratory brainstem regions.In males, aging alone reduced respiratory frequency (160.7 ± 2.7 vs. 175.5 ± 1.8 breaths/min; P = 0.003; Two-Way ANOVA), impaired the hypercapnic ventilatory response (P < 0.0001), and altered pulmonary mechanics (P < 0.05). In PD animals, aging accelerated and exacerbated dysfunction in respiratory frequency declining earlier in aged than adult mice (day 4 vs. day 8; P = 0.0367; mixed-effects models). Histological analyses revealed that aged males exhibited reduced NK1r expression in the preBötzinger complex (preBotC: -21%) and rostral ventral respiratory group (-16%), loss of Phox2b-expressing neurons in the retrotrapezoid nucleus (RTN: -34%) and reduced noradrenergic neurons in the locus coeruleus (-24%), with greater degeneration in PD animals. Aging also increased astrocyte density in respiratory brainstem regions (P < 0.05; Two-Way ANOVA). In females, aging did not affect respiratory frequency (P = 0.8398; mixed-effects models), although altered pulmonary mechanics. In females, aging did not affect respiratory frequency (P = 0.8398; mixed-effects model), although it altered pulmonary mechanics. PD-induced alterations in respiratory frequency emerged similarly in both adult and aged females from day 10 onward. Histological analyses revealed relatively mild changes, including reduced NK1r expression in the preBötC (-17%) and a decrease in RTN neuronal populations (-23%), with additional losses associated with PD.These findings demonstrated that aging increases vulnerability to PD-related respiratory dysfunction in a sex-dependent manner, with males showing earlier and more sever impairment of respiratory function and brainstem respiratory networks.

Disclosures: T.O. Macedo: None. **M. Oliveira:** None. **T.S. Moreira:** None. **A.T. Takakura:** None.

Nanosymposium

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Presentation Number: NANO22.09

Topic: C.03. Parkinson’s Disease

Support: CAPES 88887.845571/2023-00

Title: Caffeine prevents respiratory dysfunction and brainstem oxidative stress in a mouse model of Parkinson’s Disease

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Abstract: Parkinson's disease (PD) is characterized by degeneration of dopaminergic neurons in the substantia nigra, leading to motor and respiratory dysfunctions. Pharmacological treatments for respiratory symptoms remain limited. Caffeine (caf), an adenosine receptor antagonist, exhibits neuroprotective effects in PD models and may modulate breathing through actions on brainstem regions. This study investigated the effects of caffeine on respiratory dysfunction in a 6-hydroxydopamine (6-OHDA)-induced PD model. Adult male C57BL/6 mice (CEUA: 5513240518) received caffeine (0.3, 3, or 10 mg/kg) or vehicle (veh)for dose-response analysis. Behavioral assessments included the open field ($p<0.0001$), light-dark box ($p=0.3234$), elevated plus maze ($p=0.0020$), and plethysmography ($p=0.6179$), performed on the first and last experimental days. After dose definition, animals received bilateral striatal injections of 6-OHDA (10 μg/μL) or veh. Five days later, mice received daily intraperitoneal injections of caffeine (0.3 mg/kg) or veh for five days. Whole-body plethysmography was then performed to evaluate respiratory parameters and assess the potential of caffeine to modulate PD-associated respiratory disturbances. Statistical analyses included Student's t-test or one-/two-way ANOVA followed by Tukey's post hoc test. Confirming the PD model, dopaminergic neurons in the substantia nigra were reduced by more than 70% 10 days after 6-OHDA injections. Caffeine treatment prevented thereduction in respiratory rate (sham+veh: 205.9±3.1; sham+caf: 202.1±9.8; 6-OHDA+veh: 158.6±6.4; 6-OHDA+caf: 188.9±17.6 breaths/min, $p=0.0037$), and the reduction in neurokinin-1 receptor density in the pre-Bötzinger complex (pre-BötC) (sham+veh: 25.8±1.3; sham+caf: 25.8±1.5; 6-OHDA+veh: 22.3±0.2; 6-OHDA+caf: 24.5±0.7%, $p=0.0369$), but did not prevent the reduction of Phox2b positive neurons in the retrotrapezoid nucleus (RTN) of 6-OHDA animals (sham+veh: 65±9.9; sham+caf: 62.6±5.6; 6-OHDA+veh: 42.5±7; 6-OHDA+caf: 50.3±4.5, $p=0.3791$). In addition, caffeine attenuated oxidative stress in both the pre-BötC (sham+veh: 6.2±1.4; sham+caf: 5.6±0.6; 6-OHDA+veh: 10.4±1.2; 6-OHDA+caf: 7±1.4 A.U., $p=0.0009$) and RTN (sham+veh: 9.13±0.8; sham+caf: 8.5±1.2; 6-OHDA+veh: 11.7±1.3; 6-OHDA+caf: 8.3±1.1 A.U., $p=0.0004$). No significant alterations were observed in control animals receiving caffeine treatment alone. These findings highlight the therapeutic potential of subchronic caffeine treatment in preventing respiratory alterations observed in this PD model.

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Nanosymposium

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Presentation Number: NANO23.01

Topic: E.03. The Chemical Senses

Support: Leon Levy Scholarship in Neuroscience
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U19NS107464
U19NS112953

Title: Olfactory circuit mechanisms supporting temporal sequence geometry

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Abstract: Neural circuits encode sensory stimuli through structured activity patterns shaped by their connectivity. In mammalian olfaction, olfactory bulb mitral and tufted cells (MTCs) encode odors with precisely timed activity sequences that tile the respiration cycle. While these dynamics may represent an important feature of odor encoding and significantly impact perception the principles underlying the formation, structure and role of these sequences remain poorly understood. To explore this, we developed a custom 2-photon microscope capable of fast calcium imaging of hundreds of MTCs with sub-sniff resolution, as well as multiscale optogenetic interrogation of effective connectivity. The system combines large-scale patterned stimulation using a digital micromirror device (DMD) with fine-scale holographic 2-photon stimulation using a spatial light modulator, allowing us to measure the odor responses of MTCs as well as identify their feedforward and recurrent inputs. First, measuring the responses to many odors, we show that odor-evoked MTC sequences propagate as wavefronts through a low-dimensional odor tuning space, where timing is predicted by the tuning similarity between neurons rather than physical location. Second, using DMD stimulation of individual ChR2-expressing glomeruli, we identified populations of MTCs sharing common glomerular input. We compared odor response sequences between glomeruli and MTCs, revealing a general principle by which early responding glomeruli are more likely to activate their connected MTC than later responding glomeruli (see Karadas et al., Nat. Neuro., 2026). Finally, we used holographic stimulation to probe effective recurrent interactions between individual MTCs, observing both excitatory and inhibitory influences. Strikingly, we found that similarly tuned MTCs receive similar patterns of modulation from nearby MTCs, whereas differently tuned MTCs receive distinct patterns of modulation. These structured interactions are predicted to enhance correlations among similarly tuned neurons while reducing correlations among dissimilarly tuned neurons, providing a candidate circuit mechanism shaping the geometry of odor-evoked population activity and its sequential propagation through odor tuning space.

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Nanosymposium

NANO23: Physiology and Modulation of Olfactory Processing Across the Hierarchy

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Topic: E.03. The Chemical Senses

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Title: A low-dimensional code links glomerular activity to perception and predicts glomerular metamers

Authors: *W. G. BAST[1], C. AGHAMOHAMMADI[2], P. GUPTA[1], T. A. ENGEL[3], D. ALBEANU[1];
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Abstract: Olfaction still lacks a unifying circuit-level framework linking odorant receptor (OR) activity to olfactory percepts. To investigate how OR responses shape perceived stimulus similarity, we developed a novel approach that exploits the anatomical convergence of ORs onto individual glomeruli to control sensory input at the level of specific OR types. Using two-photon and widefield imaging, we identified numerous glomeruli and measured their responses to 121 odorants. We then generated synthetic olfactory stimuli by optogenetically activating selected glomerular combinations. To assess perceptual similarity, we trained mice in a novel Go/No-Go task to report perceived differences between test stimuli and a reference glomerular activation pattern. Using this approach, we found that glomeruli within the reference set differ in perceptual relevance: activation of some glomeruli elicited substantially larger perceptual changes than others. Glomerular perceptual impact correlated with similarity in glomerular odorant responses, consistent with a low-dimensional organization of olfactory representations. Using only glomerular responses to odorants, we inferred a latent perceptual space with an autoencoder objective and found that ~12 dimensions were sufficient to capture odor representations. Projections of synthetic activity patterns into this space accurately predicted behavioral responses to novel stimuli. Moreover, the low dimensionality of the latent space predicts the existence of non-overlapping glomerular activity patterns that generate indistinguishable percepts. These “glomerular metamers” were confirmed experimentally within the resolution of our assays. Our results indicate that olfactory perception is low-dimensional and inherently structured for efficient odor representation. More broadly, they support a model in which olfactory neural circuits transform high-dimensional OR inputs into a structured low-dimensional representation that links glomerular activity to perception.

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Nanosymposium

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Topic: E.03. The Chemical Senses

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Title: Locomotion modulation of sniff phase-locking and odor responses in the rodent main olfactory bulb

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Abstract: Olfactory behaviors like navigating towards an odor source or tracking an odor trail (Khan et al, 2012) require locomotion; this movement both assists in the tracking of chemosensory cues (Findley et al, 2021) but also alters those cues due to self-generated motion and changes in behavioral state. Odors are encoded through spatiotemporal patterns of activity across populations of mitral and tufted (M/T) cells in the main olfactory bulb (MOB), including precisely timed responses that are phase-locked to the sniff cycle (Shusterman et al, 2011). Furthermore, recent work has demonstrated that M/T cells are also capable of encoding locomotor information, independent of odor encoding (Chockanathan et al, 2021). Together, these findings raise two related questions: how does locomotion reshape the behavioral context in which odors are sampled, and how do these state-dependent changes shape the stability and variability of the neural responses to odors. To address these questions, we performed high-density recordings of M/T cell responses to an array of 22 monomolecular odors in the MOB of awake head fixed mice (N=5) on a freely rotating wheel. In parallel, we monitored the animal's sniffing and pupil size using a mass flow sensor and infrared camera, respectively, with pupil size serving as a proxy measure of arousal. We found that locomotion altered the behavioral context in which odors were sampled, including significant changes in the joint relationship between sniff rate and pupil size. Locomotion also shifted sniff phase-locking of individual neurons toward the exhalation onset of the sniff cycle. Lastly, while some neurons encoded odors independently of locomotor behavior, others showed significant trial-to-trial variability in responses to the same odor as a function of locomotor state. Thus, odor encoding by M/T cells in the MOB requires consideration of not only odor identity or concentration, but also the locomotor behavioral state of the animal.

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Nanosymposium

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Topic: E.03. The Chemical Senses

Support: Israeli Science Foundation grant to A. MIZRAHI (#511/23)
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Title: Late development of olfactory circuitry underlies innate behavior

Authors: *E. TAHA, S. SHAPIRA, R. NAHARI, O. YUDCO, H. SAGI, N. ASHKENAZI, M. WARBURG-GIVON, M. SHERMAN, I. SEGEV, A. MIZRAHI;
The Edmond and Lily Safra Ctr. For Brain Sci. (ELSC), The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Innate behaviors are evolutionarily conserved responses that enable animals to rapidly react to biologically relevant stimuli without prior experience. In the olfactory system, certain odors associated with food, predators, or social cues can evoke robust attraction or avoidance behaviors without prior experience, relying on genetically programmed neural circuits. In contrast, learned olfactory behaviors emerge through experience and depend on neural circuits that undergo experience-dependent plasticity. While the adult neural pathways underlying innate and learned olfactory behaviors have been extensively characterized, remarkably little is known about how innate and learning-related circuits develop, and generally when innate odor-guided behaviors first become functional. Here, we show that appetitive and aversive innate olfactory behaviors emerge surprisingly late during postnatal development. Juvenile mice exhibited weak or no responses to innately attractive and aversive odors. In contrast, juveniles displayed robust associative odor learning, indicating that circuits mediating learned and innate behaviors follow distinct developmental trajectories. Anatomical tracing revealed that projections from olfactory bulb mitral cells (MC) to the cortical amygdala (CoA), a key node mediating innate odor-driven behaviors, are structurally immature in juveniles. In contrast, projections to the anterior piriform cortex, which supports learned odor associations, exhibit earlier maturation. Importantly, selective optogenetic activation of olfactory bulb projections to the CoA was sufficient to restore adult-like innate odor preferences in juvenile mice, suggesting that pathways downstream of CoA are developmentally mature. Using in vivo two-photon calcium imaging, we examined odor representations in MC populations. We found that these representations are more promiscuous and variable in juveniles than in adults. Thus, we suggest that immature olfactory bulb circuitry contributes to less selective and less reliable innate odor information. Projection-specific imaging further revealed functional specialization among MC subpopulations: in adult mice, CoA-projecting MCs exhibited stronger and more sustained responses to innately aversive odors than piriform cortex-projecting MCs. In summary, we reveal distinct developmental trajectories for circuits mediating learned and innate olfactory behaviors and identify delayed maturation of the olfactory bulb-amygdala pathway as a key mechanism underlying the late emergence of innate odor responses.

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Title: Activity-dependent molecular signatures induced by converging olfactory and spatial inputs in the lateral entorhinal cortex

Authors: *N. L. KLIMPERT, A. FLEISCHMANN;
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Abstract: Recent advances in next-generation sequencing have enabled brain-wide characterization of neurons based on their transcriptomes: the genes a neuron expresses establish its stable cell-type identity. However, stimulus-evoked neural activity drives robust changes in gene expression, which is essential for circuit-level plasticity required for memory formation. This raises a fundamental question: How do neurons balance stable transcriptomes that define their molecular identity with diverse context and experience-dependent changes in transcription? We propose that exposure to sensory stimuli drives transcriptional changes that define a neuron's *activity state*. These activity states can reflect functional connections between brain regions, and their gene expression profiles may be critical for consolidating circuits that encode associative memories. To test this hypothesis, we investigated transcriptional changes driven by converging olfactory and spatial inputs in the lateral and entorhinal cortex (LEC), a region that integrates olfactory information from the piriform cortex (PCx) and contextual information from the hippocampus (HPC). Using a combination of chemogenetic manipulation, an olfactory-spatial behavioral paradigm, and single-nucleus RNA sequencing (snRNA-seq), we have characterized dynamic, cell type-specific, and connectivity-specific activation profiles of LEC neurons. Notably, we uncovered distinct synergistic activity states among deep layer Vb neurons, whose transcriptional responses are uniquely driven by the convergence of PCx and HPC inputs. By examining experience-induced transcription in LEC neurons following an olfactory-spatial behavioral task, we propose that these synergistic activity states may provide molecular mechanisms to support circuit strengthening underlying odor-place integration. Together, these findings advance our understanding of brain cell diversity beyond fixed transcriptional identities, revealing how transient activity states shape the molecular landscape of neurons to support circuit plasticity and experience-dependent behavioral adaptation.

Disclosures: N.L. Klimpert: None. **A. Fleischmann:** None.

Nanosymposium

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Topic: E.03. The Chemical Senses

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Koret Human Neurosciences Community Laboratory
Stanford University Bio-X Fellowship

Title: Respiratory Phase Orchestrates Human Olfactory Cortical Dynamics

Authors: *A. Y. HATHAWAY[1], T. P. COLEMAN[2];
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Abstract: Olfaction is fundamental to perception, memory, and emotion, yet the neural basis of human odor processing remains poorly understood. Here, we demonstrate that odor-evoked brain activity is organized by respiratory phase--not absolute time--revealing that natural breathing structures olfactory cortical dynamics. Using simultaneous nasal respiration and electroencephalography (EEG) recordings in 17 participants, we delivered naturalistic odors (peppermint, oregano, and grapefruit) synchronized to individual breathing cycles. Odor presentation elicited distinct, respiratory phase-locked event-related spectral perturbations (RPL-ERSPs) in frontal and temporal regions, emerging during the first breath after stimulus onset. The most discriminative neural signatures were theta-band activity during inhalation and alpha-band activity during exhalation, patterns that were obscured in traditional time-locked analyses due to natural variability in breath duration. Leave-one-subject-out cross-validation of RPL-ERSPs achieved reliable odor discrimination (peppermint: AUC = 0.78; oregano: AUC = 0.68; grapefruit: AUC = 0.61), establishing that phase-locked features generalize across individuals. To connect neural responses to perceptual experience without relying on precise odor naming—which is notoriously difficult and can be disproportionately impaired in some populations—we quantified odor recognition using free-response descriptions scored with a semantic-similarity approach. Behavioral recognition strength paralleled the neural decoding hierarchy across odors, establishing the perceptual validity of RPL-ERSPs. RPL-ERSPs also revealed rapid habituation, with decoding performance declining over repeated presentations, due to selective degradation of the most informative phase-locked features. Together, these findings establish respiratory rhythm as a temporal scaffold for human olfactory cortical processing, positioning RPL-ERSPs as a sensitive, task-free approach for assessing olfactory function. We provide an open-source, respiration-synchronized olfactometer design (<$500) to enable replication and broader adoption of this approach.

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Nanosymposium

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Topic: E.03. The Chemical Senses

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Title: Role of the mushroom body in generating stereotyped olfactory preferences in Drosophila melanogaster

Authors: A. K. GUPTA, ***N. GUPTA**;
Indian Inst. of Technol. Kanpur, Kanpur, India

Abstract: Animals rely on innate behaviors linked to foraging, courtship, avoiding danger, and nesting to increase their chances of survival and reproduction. In fruit flies, olfactory cues aid in the successful execution of some of these behaviors. Multiple factors add variability at almost every node in the olfactory circuit, including the olfactory receptor neurons (ORNs), projection neurons (PNs), local neurons (LNs), and Kenyon cells (KCs). Although one might expect the variability at all these levels to accumulate and result in inconsistent behaviors, flies must behave reliably in their environment, seeking food when hungry and avoiding aversive stimuli. The actual degree of stereotypy in the innate olfactory behaviors of individual fruit flies is unclear. We designed a T-maze assay to measure the innate olfactory preferences of individual flies for attractive and aversive odors, and found high stereotypy in odor preferences across flies. Next we sought to understand the neural mechanisms determining behavioral stereotypy. The aggregate odor responses of gamma lobe Kenyon cells (**γ**;-KCs) in the mushroom body were significantly less stereotyped than the behavior. Thus, we reasoned that the variability present till the KC layer may be compensated for in subsequent layers. Surprisingly, the odor response stereotypy was not higher in two MBONs downstream of **γ**;-KCs. We hypothesized that combinations of MBONs may be more stereotyped than individual MBONs. This was validated using connectome-restricted simulations, where the odor responses of common downstream targets of recorded MBONs had higher stereotypy than those of individual MBONs. Since MBONs' output regions overlap with the input regions of dopamine neurons (DANs), we checked if DANs also have higher stereotypy than MBONs and found this to be true for the odor responses of **γ**;2-compartment DANs. Interestingly, blocking **γ**;2-compartment DANs during behavior increased across-fly behavioral stereotypy. A connectome-restricted model of the mushroom body explained that this manipulation affects the dopamine-dependent plasticity of KC to MBON connections. Overall, this work highlights the involvement of **γ**;2-compartment DANs in regulating innate olfactory behavioral stereotypy.

Disclosures: A.K. Gupta: None. **N. Gupta:** None.

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Topic: E.03. The Chemical Senses

Support: NIH DC019124

Title: Transient functional coupling between Anterior Olfactory Nucleus and Ventral Hippocampus emerges during a contextually cued olfactory decision task

Authors: *N. AGRAWAL[1], O. D. ESCANILLA[2], D. E. SCOTT[3], L. M. KAY[7], D. M. SMITH[4], T. A. CLELAND[5], C. LINSTER[6];
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Abstract: Many animals make decisions based on learnt olfactory information. The same odor can carry very different meanings depending on the context in which it is encountered. For a rat, the smell of food may signal danger when humans are nearby but an opportunity to eat when they are not. Previous work has shown that context dependent odor perception relies on Anterior Olfactory Nucleus (AON) and ventral Hippocampus (vHC). Lesions of the AON, or of vHC projections to it, impair the formation and retrieval of context-dependent odor associations. How spatial context shapes olfactory perception in a temporal dynamic framework remains an open question. We hypothesized that functional connectivity between these two areas would increase dynamically when an animal must integrate spatial context with odor to make a decision. To test this, we used a context-dependent olfactory decision task in a three-chamber box with two distinct contexts (a black and a white chamber) and a central, neutrally colored waiting area. In each context chamber, rats chose between two differently scented odor dishes, one of which contained a food reward. In the context-dependent task, the rewarded odor was determined by the chamber's color, with opposite reward contingencies in each context. In a control, context-irrelevant task, the same odor was always rewarded regardless of the chamber's color. We recorded local field potentials (LFPs) from the vHC and AON in male rats (n = 4), tested over multiple recording sessions of 20 trials in which the two contexts were presented in randomized order. We divided each trial into a pre-door epoch (before the context was revealed), a pre-dig epoch (the decision window), and a post-dig epoch (after the choice). During the baseline period, there was no difference in oscillatory power and AON-vHC coherence between the experimental and control conditions. The difference between the two conditions emerged around the pre-dig epoch (decision window). Beta-band (12-30 Hz) oscillatory power in both the AON and vHC was higher during the pre-dig decision window than before the context was revealed, and this change occurred only in the context-dependent task (effect of epoch: AON $p = 0.019$; vHC $p = 0.017$). In line with our hypothesis, AON-vHC coherence was higher in the context-dependent task (task effect $F(1,225) = 11.711$, $p = 0.001$), carried by the beta band ($F(1,75) = 5.865$, $p = 0.018$) and restricted to the pre-dig window. This increase was confined to the pre-dig epoch and was absent in the control task. These results show that communication between AON and vHC is not a static feature of these connected circuits but is recruited transiently and on demand.

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Nanosymposium

NANO23: Physiology and Modulation of Olfactory Processing Across the Hierarchy

Location: WCC Rm 140

Time: Monday, November 16, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO23.09

Topic: E.03. The Chemical Senses

Title: Attentional Modulation of Human Single-Neuron Odour Representations

Authors: *M. S. KEHL[1], G. N. DIKECLIGIL[2], V. BORGER[3], R. SURGES[4], J. A. GOTTFRIED[2], F. MORMANN[5];
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Abstract: The same odour can be perceived differently depending on whether we notice it, ignore it, or deliberately search for it. Olfaction is fundamentally context-dependent, yet the neuronal coding mechanisms by which attention reshapes human odour processing remain unknown. Our recent single-neuron recordings revealed that neurons in the human piriform cortex and medial temporal lobe encode odour identity, revealing principles of cellular odour coding in the human brain. However, it is unclear how this code is modulated by higher-order cognitive demands and at which stage of the olfactory pathway attention exerts its influence. To address this question, we recorded single-neuron activity in patients undergoing intracranial monitoring while they performed an odour-visual attention task. On each trial, participants received identical, precisely controlled odour and visual inputs, but were instructed to attend either to the odour or to the visual cue. This design allowed us to isolate attentional modulation from sensory stimulation.
We found that odour identity was encoded fastest and most precisely by neurons in the human piriform cortex, whereas odour coding emerged later and less prominently in medial temporal lobe regions. In contrast, medial temporal lobe activity more accurately predicted the current attentional focus, suggesting that these regions integrate olfactory information with task demands. Together, these findings reveal a functional division within the human olfactory system. Piriform cortex provides a rapid and precise representation of chemical odour identity, while medial temporal lobe circuits flexibly link odour information to attentional focus. Our results show how cognition dynamically reshapes sensory coding in the human brain.

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Nanosymposium

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Presentation Number: NANO23.10

Topic: E.03. The Chemical Senses

Support: Israel Science Foundation program [1211/25].

Title: Encoding Context-Dependent Stimulus Statistics

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Abstract: Animals continuously estimate the statistics of sensory events in their environment to guide behavior. Yet, how the brain constructs internal models that represent the probability distributions of stimuli through learning, how these models are updated during rapid contextual shifts, and what brain regions integrate contextual and probabilistic information remains unclear. Here, we devised a behavioral task in which mice used rapidly changing contextual information to estimate the probability of upcoming odors. Recordings from the piriform and orbitofrontal cortices during learning revealed two distinct neuronal subpopulations that differentially encoded odor probabilities. One subpopulation exhibited ramping activity that scaled with the estimated probability of the behaviorally relevant odor and sharply dropped at its onset. In contrast, a second subpopulation became active at odor onset and was modulated by prediction. Notably, probability information emerged in the orbitofrontal cortex before the piriform cortex, and silencing the orbitofrontal cortex abolished the propagation of this information to the piriform cortex, impairing probability learning and retrieval but not context identification. These findings reveal a frontal-sensory circuit that facilitates the learning and representation of context-dependent, behaviorally relevant event probabilities, and suggest that learned state transitions, a core feature of a cognitive map, are propagated to the sensory cortex through learning.

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Nanosymposium

NANO24: Neuroprosthetics: Motor Control

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Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.01

Topic: F.05. Brain-Machine Interface

Support: DoD CDMRP SCIRP SC180308
VAMR 5I01RX002654
NIH T32EB004314

Title: Constructing Optimal Peripheral Nerve Stimulation Patterns to Restore Hand Function

Authors: *B. ALEXANDER[1,2,3], T. JOHNSON[1,3], R. ADAMS[3], W. MEMBERG[1,3], R. F. KIRSCH[1,2,3], E. L. GRACZYK[1,2,3], E. HERRING[4], J. SWEET[4], S. BAZAREK[4], B. AJIBOYE[1,2,3];

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Abstract: The Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial uses implanted electrodes in the brain and arm to restore communication between the central and peripheral nervous systems of human participants after cervical spinal cord injury (SCI). The multi-contact nerve cuff electrodes in the arm use functional electrical stimulation (FES) to reanimate the fingers, wrist, and arm to restore reaching and grasping movements. Efficient calibration of optimal FES patterns has long been a challenge for the field. Historically, experts have constructed stimulation patterns using physiological knowledge and a limited set of recruitment curves (RCs). Our 16 contact nerve cuff electrodes result in over 200 possible bipolar stimulation combinations. Since pulse amplitude (PA) and pulse width (PW) both modulate intensity of activation, there is also a massive stimulation space that can be explored for each electrode combination. We have previously developed and validated a characterization method based on the strength-duration curve that constructs a full model of the PA/PW stimulation space in just 12 sampled EMG points. This allows for the rapid selection of the ideal RC slope and ideal muscle selectivity. Using this method, we characterized different anode-cathode combinations on the radial and ulnar nerve cuffs in a 34 year old male participant with a motor complete C3/C4 SCI. For each contact that we cathodically stimulated, changing the anode resulted in changes in recruitment order and the maximally activated muscle. We evaluated muscle selectivity for these cathode-anode combinations using the selectivity index (SI), which is the normalized activation of the muscle of interest minus the average normalized activation of all other muscles. We found that the average maximum SI went from 0.42 to 0.50 for the ulnar nerve and 0.40 to 0.46 for the radial nerve. While some muscles were already maximally selective using the initial subset, half of the muscles had an increase of more than 0.05 and 2 of the 14 muscles saw improvements of about 0.20. We then used visual and kinematic measures to test the electrode combinations with the best selectivity and the PAs that produced PW-modulated RCs with the best slopes. The settings that evoked the most optimal movements were used to construct functional hand grasp patterns that allowed for good control of the fingers, thumb, and wrist. The calibration pipeline we have established is an efficient framework for the construction of functionally useful stimulation patterns for FES neuroprostheses, improving selectivity and control while minimizing the amount of time experts need to spend on exploration and testing.

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Nanosymposium

NANO24: Neuroprosthetics: Motor Control

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Presentation Number: NANO24.02

Topic: F.05. Brain-Machine Interface

Support: NRRP Grant PE0000006
NRRP Grant IECS00000017
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Title: Targeted nerve stimulation to restore single-finger movements after spinal cord injury: computational and first-in-human clinical evidence

Authors: *E. LOSANNO[1], F. AGNESI[4], G. RIGHI[5], M. BIONDI[5], S. ROMENI[6], C. VERARDO[1], N. GIANNOTTO[7], J. MARTENS[8], F. I. SERDANA[9], V. FOSSATI[2], R. FERRONI[1], P. CVANCARA[8], J. CARPANETO[3], P. BIGAZZI[5], T. STIEGLITZ[10], G. DEL POPOLO[5], S. PFANNER[5], S. SHOKUR[11], S. MICERA[12];
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Abstract: Recovery of hand mobility is a fundamental need for individuals with tetraplegia due to spinal cord injury. Although current neurotechnologies can restore some grasping functions, they remain far from reproducing the full dexterity of the human hand. Achieving dexterous control requires the selective recruitment of individual muscles to independently move each finger. In this study, we explored targeted nerve stimulation via intrafascicular electrodes in restoring single-finger movements. To support clinical translation of this technique, we exploited biomechanical analysis, surgical mapping, and computational modeling. First, we identified the extrinsic hand muscles responsible for isolated finger movements and the corresponding motor branches of the median and radial nerves as optimal implantation targets. We then developed a hybrid computational model combining neuroanatomical and biomechanical simulations to evaluate whether stimulation of these branches via intrafascicular electrodes could achieve selective finger control across individuals. The model predicted robust kinematic selectivity under a wide range of nerve topographies and electrode placements. Supported by these computational results, we conducted a first-in-human clinical study in a participant with chronic motor-complete tetraplegia. Over a two-month testing period, targeted intrafascicular stimulation restored highly selective hand movements consistent with model predictions. Stimulation of the median nerve enabled independent flexion of the thumb, index, middle, and ring fingers, while stimulation of the radial nerve elicited isolated thumb extension and hand opening. By combining single-finger flexion movements, we successfully restored the lateral, hook, and palmar grasps. The grasp force could be smoothly controlled by modulating the stimulation parameters and could be sustained for functional periods of time. Finally, we measured the participant's functional recovery when voluntarily triggering the restored grasps via a button.

With the aid of stimulation, the participant substantially improved his performance in the box-and-block and nine-hole peg tests and regained the ability to perform daily tasks such as pouring water from a bottle, opening jars, and manipulating coins. Together, these findings demonstrate the feasibility of restoring dexterous hand control through targeted intrafascicular stimulation, potentially offering transformative benefits for individuals with spinal cord injury.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

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Michigan Medicine Neurosurgery Department

Title: Investigating Functional Electrical Stimulation Control of the Upper Limb Using Intramuscular and Direct Motor Point Targeted Electrodes

Authors: *M. KELBERMAN[1], A. WARD[1], M. MENDER[3], J. DEMATTEO[4], J. JOSEPH[4], H. TEMMAR[2], I. TOWNE[4], J. LAM[5], N. GANESH KUMAR[9], T. A. KUNG[6], Y. SAADEH[7], C. A. CHESTEK[8];
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Abstract: Upper limb paralysis affects millions worldwide. Brain computer interfaces (BCI) can extract motor control signals from the brain and have been used to control cursors or robotic hands. Another promising use is controlling the patient's paralyzed hand directly through functional electrical stimulation (FES). Recent BCI advances mean that systems are now limited by FES quality rather than the control signals. One limitation is the lack of movement specificity produced by certain stimulation targets (nerve cuffs, intraneural electrodes). Biomechanical

constraints of controlling highly linked joints in the hand also create limitations. There is a need for better targets and training techniques to design FES capable of restoring dexterous hand control.
To improve FES targeting, we developed a novel technique inserting intramuscular electrodes adjacent to the nerve entry points of the extrinsic hand muscles (direct motor point (dmp) FES) in a rhesus macaque model. One macaque was implanted with 16 bipolar dmpFES targeted electrodes. This was twice the amount we had implanted in a prior macaque with muscle belly targeting (Nason et al. 2023). We stimulated both subjects under nerve block to investigate movements on a single electrode basis. We generated detailed characterization of the response to increased charge delivery. We also studied the continuous, simultaneous control of the wrist and fingers.
We found that dmpFES enables mostly highly specific movements in the wrist during increased charge delivery. Finger movements were specific at low current delivery, though higher currents recruited the wrist via biomechanical coupling. Active muscle recruitment appeared precise to the target. Preliminary evidence suggests that dmpFES may offer improved fatigue resistance. We theorize that this is due to dmpFES recruiting more slow twitch muscle fibers. The response of both implant styles to a sweep of increasing stimulus followed predicted anatomical function. It also followed a characteristic pattern and was well approximated by a sigmoid function. Simultaneous target-based control of the wrist and fingers for both subjects resulted in an 85.5% target acquisition success rate in the middle half of the available range of motion.
We successfully characterized movements for both intramuscular and dmpFES in rhesus macaques. Because each extrinsic hand muscle contains 2-5 motor points, dmpFES may be key to improving FES. If all of these were implanted in a high channel count stimulation system, the most advantageous electrode or combination of electrodes could be sampled and utilized for muscle control under the control of interfaces like BCIs.

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Nanosymposium

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Presentation Number: NANO24.04

Topic: F.05. Brain-Machine Interface

Support: CDMRP SCIRP W81XWH-22-1-1119
CDMRP SCIRP W81XWH-22-1-1083

Title: A High-Density EMG-FES Forearm Wearable for Use in Neurorehabilitation

Authors: *D. A. FRIEDENBERG[1,2], L. WENGERD[3], S. CADY[2], B. SCHLINK[2], C. DUNLAP[2];
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Abstract: Individuals with spinal cord injury (SCI) and stroke experience severe motor and sensory impairments that alter their daily functioning. Loss of hand function significantly impacts the ability to perform activities of daily living, affecting quality of life and autonomy. To address these challenges, functional electrical stimulation (FES) is a widely used noninvasive rehabilitation technique that delivers electrical pulses to muscles, thereby inducing targeted contraction in paretic muscles. Recent advances in FES have incorporated electromyography (EMG) signals into a closed-loop feedback system. EMG serves as an indicator of voluntary motor intent, and when integrated with FES, allows for the user to modulate muscle activity in real-time. We hypothesize this EMG-controlled FES closed loop approach could improve outcomes in SCI and Stroke rehabilitation by promoting more natural and coordinated muscle activation patterns. We are conducting preliminary studies to evaluate the feasibility of using a novel high-density electrode forearm sleeve that integrates EMG and FES in a closed loop system as a rehabilitative tool in individuals with chronic SCI and Stroke. Participants who have completed the study have reported improvements in their ability to perform tasks independently after using the system including increased hand strength, coordination, and flexibility in their paretic hand. Furthermore, analysis of the high-density EMG data provides a unique window into potential changes in muscular activation patterns and neuromuscular connectivity. Our findings highlight the potential of our high-density EMG-FES system to decode residual motor activity from the paretic arm, leverage these neural signals to facilitate functional motor recovery, and drive neuroplasticity following neurological injury.

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Nanosymposium

NANO24: Neuroprosthetics: Motor Control

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Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.05

Topic: F.05. Brain-Machine Interface

Support: New York State Spinal Cord Injury Research Board

Title: Intra- and Interhuman BCI-Based Interventions for Sensorimotor Restoration in Tetraplegia

Authors: *C. BOUTON;
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Abstract: Severe cervical spinal cord injury (SCI) disrupts distributed sensorimotor networks, causing lasting deficits in movement and sensation. We tested whether closed-loop neural bypasses linking cortical activity to targeted neuromodulation of the spinal cord, peripheral nervous system, and somatosensory cortex could restore immediate and durable motor and sensory function after chronic SCI. In a first-in-human clinical study, a participant with chronic motor- and sensory-complete cervical SCI was implanted with intracortical microelectrode arrays in primary motor (M1) and primary somatosensory (S1) cortices. Movement intent was decoded in real time to control patterned stimulation of the spinal cord and upper-limb muscles. For sensory recovery, activity recorded during sensory imagery and observation guided intracortical microstimulation of S1 ("cortical mirroring") combined with targeted spinal cord stimulation. Outcomes during and after use of the **'double neural bypass' (DNB)** system were assessed longitudinally. Patterned spinal modulation was associated with greater voluntary muscle activation and recovery that persisted for more than three years. Sensory interventions improved tactile perception and sensorimotor cortical activity for more than two years, even with the DNB was turned off for months. In a second portion of the study, cortical signals from one implanted BCI participant with SCI were decoded and transmitted to a second participant with SCI to restore immediate and recovered hand movements and strength through a custom, wireless high-resolution neuromuscular stimulation device and modulated transcutaneous spinal cord stimulation. This approach produced significant functional gains and more than a twofold increase in hand strength. Improvements beyond active device use suggest therapy-induced neuroplasticity in residual sensorimotor pathways. These findings show that distributed bioelectronic neural bypasses linking brain activity to spinal, peripheral, and cortical neuromodulation can provide both assistive and restorative benefits after severe SCI, supporting future individual **and cooperative** neurorehabilitation strategies that engage motor and sensory networks to drive durable recovery.

Disclosures: C. Bouton: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sanguistat. Other; Neuvotion.

Nanosymposium

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Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.06

Topic: F.05. Brain-Machine Interface

Support: Christopher and Dana Reeve Foundation (Grant #002-RGC)

Title: Data-driven epidural electrical stimulation and implanted brain-computer interface to restore upper limb motor function after tetraplegia

Authors: *F. CIOTTI[1], T. COLLIN[2], I. YU[2], I. SAKR[2], S. HERNANDEZ CHARPAK[2], V. SPAGNOLO[2], L. COQUOZ[2], G. D. DUMONT, Esq.[2], G. CARPARELLI[2], P. CARVALHO[2], V. ROUANNE[2], P. FORERO[2], B. SCHORNSTEIN[2], M. PICEK[2], S. DAHAN[2], I. TOYE[2], M. AVERY[2], N. HANKOV[2], N. INTERING[2], C. DESCHENAUX[2], J. BLOCH[2], G. COURTINE[2], H. LORACH[2];
[1].NeuroRestore / Univ. of Lausanne, Lausanne, Switzerland; [2].NeuroRestore, EPFL/CHUV/UNIL, Lausanne, Switzerland

Abstract: Cervical spinal cord injury disrupts the signals between the brain and the region of the spinal cord that coordinates arm and hand movements, causing paralysis. Here we present the design and ongoing clinical trial results of a system suited for long-term chronic implantation comprising an electrocorticography-based brain-computer interface to detect motor intention from the sensorimotor cortex, and epidural electrical stimulation of the spinal cord to restore the intended movement in patients with severe motor disabilities, thereby realizing a Digital Bridge over the injured motor pathways. The recording and stimulation systems are fully implanted and interact with wearable power and control hardware wirelessly. We hereby present the results with the three individuals with chronic incomplete tetraplegia who have completed the main study phase. A decoding pipeline incorporating a foundation model of human brain activity predicted up to 8 motor states with high accuracy. In turn, linking decoding predictions to the modulation of stimulation patterns enabled the three participants to perform functional tasks with their otherwise paralyzed arm and hand. Given the complexity of upper limb movements, and the non-trivial outcome of epidural electrical stimulation, we developed new methods to exploit large multi-modal datasets collected during the trial to characterize the outcomes of the stimulation, which unvelied functional patterns that were imperceptible to the experimenters' eyes, which we exploited to optimize complex stimulation protocols to perform functional tasks. These newly developed methods might be translatable to other applications in the neuromodulation field. The Digital Bridge has remained stable for more than one year, and has been compatible with long-term stability and safety. While additional technological developments and clinical validations in a diverse patient population are required, these results establish essential concepts to enable arm and hand movements in humans living with chronic tetraplegia.

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Nanosymposium

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Presentation Number: NANO24.07

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS 5UH3NS103863-04

Title: An Implanted Networked Neuroprosthesis for Upper Limb Function in Individuals with Cervical Spinal Cord Injury

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Abstract: Implanted neuroprostheses significantly enhance independence and community participation for individuals with cervical spinal cord injuries (SCI). We developed the Networked Neuroprosthesis (NNP),a fully implanted modular system that stimulates paralyzed muscles and records voluntary myoelectric signals to provide functional grasp, release, overhead reach, and trunk stability. To evaluate the system, we initiated a pivotal, prospective, non-randomized, single-arm trial for participants with C5-C7 AIS A-C SCI. Following NNP implantation, participants undergo functional training and assessments at 3, 6, and 12 months, serving as their own controls with the system turned on versus off. The primary outcome measure is the Grasp and Release Test (GRT) to evaluate manipulation skills and strength. Secondary outcomes include the Canadian Occupational Performance Measure (COPM), the Activities of Daily Living Abilities Test (ADLAT), and qualitative interviews, which are analyzed using nonparametric sign test, hierarchical activity analysis, and thematic analysis mapped across the International Classification of Functioning, Disability, and Health (ICF) domains. Preliminary results from the first 10 participants demonstrate significant functional improvements. With the NNP turned on, participants successfully manipulated 4-6 out of 6 GRT objects, compared to just 0-2 objects prior to surgery or when the system was turned off. Furthermore, all 10 participants demonstrated increased lateral and palmar five-finger pinch strength, alongside improved COPM performance and satisfaction scores relative to baseline.

Emerging qualitative themes highlight positive surgical decision-making, smooth post-operative adaptation, excitement over restored hand movement, and successful incorporation of the device into daily routines. Long-term evaluation and enrollment are ongoing. In conclusion, the NNP is the first fully implanted, modular neuroprosthesis designed to restore multiple coordinated functions without cumbersome external components. Preliminary results indicate that the NNP provides maximum grasp benefit compared to existing alternative approaches, substantially enhancing user independence and functional ability across all three ICF domains.

Disclosures: A.M. Bryden: A. Employment/Salary (full or part-time):; The MetroHealth System. 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.; Case Western Reserve University. **M. Moynahan:** None. **K. Walsh:** None. **M. LaFave:** None. **K. Chepla:** None. **H. Hoyen:** None.

Nanosymposium

NANO24: Neuroprosthetics: Motor Control

Location: WCC Rm 145

Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.08

Topic: F.05. Brain-Machine Interface

Support: NIH DP5-OD029571
Meta Reality Labs Award #2990450277899571
NSF #2437374

Title: Somatotopic haptic feedback on the fingers and hand via a non-invasive wrist-worn neural interface

Authors: *A. HARRISON[1], T. TULLY[2], M. TROUT[3], R. URBAN[4], K. HANSEN[7], R. MADSEN[5], J. A. GEORGE[6], M. TERAMOTO[4];
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Abstract: Haptic interfaces for the hand traditionally involve a glove or handheld controller that encumbers the hand, limiting endogenous sensorimotor function. Here, we demonstrate the ability to provide somatotopic haptic feedback on the hand through a noninvasive multichannel wrist-worn neural interface. Transcutaneous electrical nerve stimulation (TENS) was used to selectively steer current to the nerves innervating the hand to create distally referred, localized sensations. These localized sensations collectively provide near complete coverage of the palmar aspect of the hand and fingers. Tripolar current steering (1 cathode, 2 anodes) was used to improve specificity relative to traditional bipolar stimulation (1 cathode, 1 anode); tripolar

stimulation yielded percepts that were significantly smaller ($p<0.010$), more distal ($p<0.004$), and more intense ($p<0.049$). Percepts were rated as mostly comfortable and somewhat natural across a broad range of tested stimulation parameters. Perceived intensity was quantified using just-noticeable differences, Weber fractions, and free-magnitude intensity tracking tasks for pulse amplitude (PA), pulse width (PW), and pulse frequency (PF). Differences in perceived intensity among PA, PW, and PF were reconciled using a new equation for Activation Charge Rate based on Steven's Power Law, which describes how different combinations of TENS parameters influence the resulting percept intensity. This equation suggests that TENS can theoretically convey the magnitude of tactile stimuli using 59 distinct perceptual intensities. With wrist TENS, participants transferred virtual fragile objects with fewer 'breaks' ($p<0.001$) and lower applied forces ($p<0.001$). Participants also discriminated among different virtual surfaces and textures by touch alone at a rate significantly greater than chance. Using multichannel stimulation, participants differentiated the direction of a sweeping sensations across their hands with a JND of 39.9 ms, with respect to a timing delay between channel stimulation onsets. Finally, we introduce a wireless, wrist-worn multichannel stimulator that packs ±135 V compliance, 4.21 billion electrode configurations, and MHz stimulation capabilities into a 24 square-cm watch formfactor. This work documents the fundamental psychometric capabilities, theoretical limits, functional benefits, and feasibility of TENS at the wrist for somatotopic haptic feedback on the hand. These findings support TENS as a non-restrictive haptic interface for augmented and virtual reality, and can guide future research in sensory restoration to partial-hand amputees.

Disclosures: A. Harrison: None. **T. Tully:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventors on a provisional patent regarding the stimulator used in this work. **M. Trout:** None. **R. Urban:** None. **K. Hansen:** None. **R. Madsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventors on a provisional patent regarding the stimulator used in this work. **J.A. George:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventors on a provisional patent regarding the stimulator used in this work. **M. Teramoto:** None.

Nanosymposium

NANO24: Neuroprosthetics: Motor Control

Location: WCC Rm 145

Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.09

Topic: F.05. Brain-Machine Interface

Support: Ohio Department of Higher Education - Spinal Cord Research
Case Coulter Translational Research Program, Phase II Award

Title: KeyGrip: A simplified implantable neuroprosthesis for hand grasp in spinal cord injury

Authors: *M. MOYNAHAN[1], H. HOYEN[1], A. BRYDEN[2], K. CHEPLA[1], K. WALSH[1], M. LAFAVE[1];
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Abstract: Neuroprosthetics that activate paralyzed muscles to restore hand function to people with cervical spinal cord injury (SCI) offer users excellent improvements in grip strength, hand function, activities of daily living, and quality of life. Earlier-generation neuroprosthetics are no longer commercially available, in part due to implant complexity and challenges with adequate reimbursement. We have developed a simple implantable functional electrical stimulation (FES) system for hand grasp ("KeyGrip") that is optimized for commercialization. We interviewed over four dozen stakeholders (clinicians, engineers, industry experts, and people with lived SCI experience) to inform the final design specifications, including: 1) limiting the number of components to permit implantation in an outpatient procedure; and 2) providing lateral pinch as the single grasp option. We identified a commercial system (Nalu Medical Peripheral Neurostimulation System) that closely matched the design specifications, designed custom electrodes, and received FDA IDE approval to begin studying the system clinically. To establish proof of concept, we measured lateral pinch force and Grasp-Release Test (GRT) performance in four individuals (5 arms) with earlier-generation implantable neuroprosthetics reprogrammed to only use 2-3 electrodes. Across the cohort, the mean increase in pinch force was 6.97 ± 2.95N with the device on. In addition, 4 out of 5 arms tested demonstrated an improvement on the GRT of at least 1 object. To demonstrate the KeyGrip system itself, we have consented three participants, and have enrolled the first individual (KG01) into the study. At the pre-surgery baseline evaluation, KG01 had a baseline pinch force of 0.0N and was unable to manipulate any of the GRT objects. The surgery included a stimulated tendon transfer to offer wrist stability, and implantation of the KeyGrip receiver and four electrodes in the following muscles: ECU, AdP, FDP, and EPL/EIP. The surgery was successfully completed as an outpatient, same-day procedure. At the 8-week visit, an exercise program was established, and KG01 is currently undergoing exercise and functional training with the KeyGrip system. In conclusion, our preliminary experience with 2- and 3-electrode configurations for lateral pinch demonstrated proof-of-concept for a simpler design. Our first-in-human experience has demonstrated the ability to implant a neuroprosthesis for hand function in an outpatient procedure.

Disclosures: M. Moynahan: None. **H. Hoyen:** None. **A. Bryden:** None. **K. Chepla:** None. **K. Walsh:** None. **M. LaFave:** None.

Nanosymposium

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Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.10

Topic: F.05. Brain-Machine Interface

Support: DoD Grant W81XWH-20-PRMRP-IIRA

Title: A Muscle Cuff Regenerative Peripheral Nerve Interface Amplifies Volitional Motor Signals for Advanced Exoskeleton Control

Authors: *Y. TIAN[1,2], A. RASTEGAR[3], C.-H. LEE[3], M. WANG[3], W. ADIDHARMA[3], M. NICOVIC[2], C. DEAN[2], A. HUSSEIN[4], A. WIERENGA[5], L. STONEBACK[6], R. KODALI[3], K. BURKE[3], H. KUPERUS[7], A. SNYDER-WARWICK[3], B. GILLESPIE[8], L. LEPLEY[6], P. CEDERNA[3], S. W. KEMP[3];
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Abstract: Foot drop is a common clinical problem characterized by impaired foot dorsiflexion, increasing the risk of unstable gait and falls. Restoring voluntary motor control remains a critical challenge. Although exoskeletons offer a promising avenue for functional assistance, current control interfaces are often limited by instability and poor-quality motor signals from the peroneal nerve. To address this limitation, the Muscle Cuff Regenerative Peripheral Nerve Interface (MC-RPNI) was developed as a biologic construct that amplifies efferent motor signals through regeneration and muscle reinnervation, providing improved control signals for exoskeletons. In this study, we evaluated MC-RPNI signal amplification, gait-correlated neural activity, and whether MC-RPNI signals were physiologic and reflected volitional motor activity rather than artifacts. In a rat model (n=6), MC-RPNIs were created using donor muscle grafts wrapped around the intact common peroneal (CP) nerve. Treadmill-trained rats were implanted with recording electrodes in the MC-RPNI, distal extensor digitorum longus, adjacent vastus lateralis and biceps femoris muscles, and cuff electrodes on the CP nerve. CP nerve, MC-RPNI, and muscle signals were recorded during treadmill locomotion while gait was simultaneously tracked using OptiTrack. Following in vivo recordings, MC-RPNIs were harvested for histological analysis using hematoxylin and eosin (H&E) and immunohistochemistry (IHC). All MC-RPNIs remained healthy with no evidence of pain, motor deficits, gait impairment, or distal muscle dysfunction. Simultaneous CP nerve and MC-RPNI recordings demonstrated greater than tenfold amplification of volitional CP nerve signals, achieving a signal-to-noise ratio of 20 dB. MC-RPNI activity was predominantly observed during the dorsiflexion phase of gait, indicating successful transduction of CP nerve activity associated with dorsiflexion motor commands and confirming the MC-RPNI as a biologic amplifier of volitional motor signals. MC-RPNI recordings exhibited a unique signal profile compared with adjacent muscles and baseline recordings, supporting a physiologic rather than electrical artifact origin. H&E staining demonstrated well-preserved muscle architecture without degeneration or neuroma formation, while IHC confirmed robust reinnervation and healthy neuromuscular junctions. The MC-RPNI reliably amplifies volitional motor signals from the CP nerve and exhibits physiologic signaling during gait. These findings support the potential of the MC-RPNI as a robust biologic interface for intuitive exoskeleton control in individuals with foot drop.

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Nanosymposium

NANO24: Neuroprosthetics: Motor Control

Location: WCC Rm 145

Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.11

Topic: F.05. Brain-Machine Interface

Title: Restoring Motor Function After Stroke Through Cervical Spinal Cord Stimulation

Authors: *L. BORDA[1], D. J. WEBER[2];
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Abstract: Stroke remains a leading cause of long-term disability, with chronic upper-limb impairments arising from disruption of corticospinal pathways and maladaptive changes within spinal sensorimotor circuits. Epidural cervical spinal cord stimulation (SCS) has recently emerged as a promising neurotechnology capable of immediately improving voluntary arm and hand function in individuals with chronic post-stroke hemiparesis. Although SCS is traditionally thought to facilitate movement through excitatory recruitment of spinal motoneurons, the broader neural mechanisms underlying its therapeutic effects remain poorly understood.Here, we investigate how SCS modulates spinal sensorimotor networks and how these changes contribute to restoration of motor control after stroke. We demonstrate that SCS engages Ia-mediated reciprocal inhibitory pathways, strengthening inhibition of antagonist muscles during voluntary reaching. We show that, in individuals with chronic stroke, enhanced reciprocal inhibition was associated with reduced abnormal co-contraction, suppression of antagonist motoneuron excitability, and improvements in movement speed and smoothness. These findings suggest that SCS restores a more physiological balance between excitatory and inhibitory spinal circuitry rather than simply increasing spinal excitability.To facilitate clinical translation, we also addressed a major challenge in neuromodulation: selection of stimulation parameters. We present a Gaussian process-based Bayesian optimization framework designed to efficiently identify stimulation parameters that maximize motor performance. This approach provides a principled strategy for patient-specific tuning and reduces reliance on empirical trial-and-error programming.Together, these findings provide mechanistic insight into how SCS restores motor function after stroke and offer a foundation for the development of individualized neuromodulation therapies for neurorehabilitation.

Disclosures: L. Borda: None. **D.J. Weber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReachNeuro, Inc.

Nanosymposium

NANO24: Neuroprosthetics: Motor Control

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Time: Monday, November 16, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO24.12

Topic: F.05. Brain-Machine Interface

Title: A Brain-to-VLA Framework: Translating Cortical Activity into Embodied Robotic Action

Authors: *W. LEE[1], **Y. LI**[2], B. LIU[3];
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Abstract: Brain-machine interfaces (BMIs) conventionally decode motor cortical activity into continuous kinematic commands, achieving accurate control in fixed settings but offering limited generalization to new task geometries, obstacles, or affordances. We investigated whether grasping intent can instead be cast as discrete semantic decisions—where to reach and what to grasp—and whether an embodied autonomous controller that acts on these decisions improves robustness. In an offline analysis of a nonhuman-primate reaching/grasping dataset, Utah array spikes were converted to firing rates; a temporal convolutional network (TCN) inferred discrete reach direction (95%, 8-class) and a winner-take-all mechanism identified the target object (91%, 3-object), forming a compact intent code. From this code, an Action Chunk Transformer generated the grasp trajectory chunk-by-chunk without an explicit planner. Compared with a conventional continuous decoder, this discrete-intent-driven framework produced more decisive trajectories (path straightness 18%, velocity zero-crossings 43%), recovered faster from target perturbations, and maintained >90% grasp success under severe channel dropout and compressed time windows, whereas the continuous decoder fell below 50%. Gains arose from the joint constraint of discrete intent and chunk-wise action generation, which steered decoding toward physically realizable paths and internalized planning. The results support the view that embodied execution structure provides an effective scaffold for interpreting motor cortical population activity. More broadly, this work reframes BMI decoding as co-adaptive intent understanding and autonomous execution: spikes supply intention-specific signals, while the discrete-intent-to-action mapping confers generalization, perturbation tolerance, and agency.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

Support: HE EIC Pathfinder/101070891 2022, NEMO BMI
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Title: Toward neuroprosthesis for everyday use: brain signal decoding to enable real-life motor tasks in motor disable subjects from chronic fully implanted ECoG recorder

Authors: *T. AKSENOVA[1], F. MARTEL[2], M. JUSTINO[2], L. STRUBER[2], A. CARVALLO[2], R. SOURIAU[2], T. COLLIN[3], V. SPAGNOLO[5], I. SAKR[6], M. ETIENNE[2], A. BLEUZÉ[2], S. KARAKAS[2], M. FILIPPI[2], J. PORCHEROT[2], F. SAUTER-STARACE[2], J. BLOCH[7], H. LORACH[4], G. COURTINE[8], G. CHARVET[2];
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Abstract: To be applicable in everyday life for the restoration of functional abilities in motor-disabled subjects, Brain-Machine interfaces should allow decoding of intended movements relevant to daily-life activities from stable and easy to use recording system. Using the chronic fully implanted WIMAGINE electrocorticography (ECoG) recording device, we investigated neuronal patterns decoding related to real-life tasks: lower limbs decoding to activate epidural electrical stimulation (EES) for natural walk restoration, decoding of uni / bimanual grasp for object manipulation using surface Functional Electrical stimulation (sFES), and, finally, in the outlook of peripheral nerves stimulation or sFES for fine pinch, the bimanual individual fingers attempted movement decoding. Stable 3-state decoding of stepping attempts in asynchronous mode was used to restore walking in laboratory, at home and outdoors in 3 participants with chronic spinal cord injury (Clinical trials (CT) STIMO-BSI, NCT04632290, and Think2Go, NCT06243952). We demonstrated that unsupervised real-time domain adaptation allows stable decoding during long period (up to 4.5 months) without performance degradation. The sample-based performance (Balanced Accuracy, BA) was 0.53, 0.61, and 0.73 in average for the 3 participants, respectively. Uni / bimanual control of a sFES device allowing grasping, pinching and hand opening actions for object manipulation using adaptive independent decoders were demonstrated in 2 tetraplegic users (CT BCI&Tetraplegia, NCT02550522). They achieved sample-based BA of 0.72 and 0.80 for unimanual control (3 classes) and 0.58 and 0.68 for bimanual control (6 and 7 classes) per participant, allowing them to manipulate objects of different forms, sizes and weights (cubes, balls and sticks). Finally, we demonstrated that our decoding framework supports fine motor decoding of uni / bimanual individual finger attempted

activation in asynchronous mode. Tested in 4 tetraplegic users (CT BCI&Tetraplegia, and UP2, NCT05665998), the sample-based BA achieved 0.70, 0.46,0.68 and 0.56 for 5 fingers and idle state decoding (6 classes), for 4 participants, and 0.70 for 10 fingers and idle state (11 classes) for 1 user. 10 fingers decoding were studied in 1 subject, as only one participant was implanted bilaterally.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

Support: Horizon-EIC-2021-Pathfinderchallenges-01-02 NEMO-BMI (101070891)
Horizon-EIC 2021-TransitionChallenges-01-01 ReverseParalysis 101057450
Carnot Leti Institute

Title: ECoG-Based BCI Platform with Embedded Neural Processing for Autonomous Home Use

Authors: F. SAUTER-STARACE[1], M. BOSQUET[1], S. KARAKAS[1], C.-E. GOUJON[2], J. PORCHEROT[1], M. FILIPPI[1], F. MARTEL[1], T. AKSENOVA[1], A. EVANS[3], ***G. CHARVET**[4]; [1]Univ. Grenoble Alpes, CEA, LETI, Clinatec, Grenoble, France; [2]Univ. Grenoble Alpes, CEA, DRT, grenoble, France; [3]Univ. Grenoble Alpes, CEA, LIST, Grenoble, France; [4]Univ. Grenoble Alpes, CEA, LETI, CLINATEC, MINATEC, Grenoble Cedex 9, France

Abstract: Brain-Machine interfaces (BMIs) have demonstrated efficacy in clinical trials, enabling individuals with severe motor disabilities to regain motor functions through the control of external effectors. However, transitioning these technologies from controlled laboratory environments to autonomous home use introduces significant challenges regarding user independence and long-term acceptance. Current clinical platforms depend on high-performance computers with a power consumption of ~30 W, resulting in bulky setups that limit patient autonomy under real-world conditions. To enhance user adoption, it is necessary to develop lightweight, ergonomic, and highly integrated systems capable of operating safely and independently in non-clinical environments. To address these limitations, a wearable platform

was developed around the WIMAGINE 64-channel wireless electrocorticography (ECoG) implant. A compact base station, named WiCAP, was integrated into standard cap to optimize wireless power transfer and bidirectional communication while ensuring patient comfort.Experimental validation demonstrated stable 64-channel ECoG acquisition with WiCAP over a 250 kb/s UHF link with a total power consumption below 1.5 W, representing an order-of-magnitude reduction compared to the 15 W required by the first-generation clinical base station. Concurrently, the clinical software suite was restructured into a modular, cross-platform architecture. Critical real-time acquisition and decoding tasks were optimized into C++ libraries, enabling deployment on a low-power embedded computing platform (Raspberry Pi 4, ~3 W). To achieve ultimate system miniaturization and full portability, ongoing efforts focus on the development of a dedicated Application-Specific Integrated Circuit (ASIC) for neural decoding to perform real-time signal processing (inference). This embedded BCI decoding chip might be integrated within the WiCAP system, eliminating the need for external computing resources. The power consumption of the decoding ASIC targets a power budget of ~10 mW, enabling fully integrated, low-power operation. This platform is designed for deployment across ongoing and future clinical trials using the WIMAGINE implant technology, including studies targeting BCI-assisted neuroprosthetic approaches or gait restoration through brain-spine Interface (BCI&Tetraplegia NCT02550522 , Think2Go, NCT06243952) and upper-limb motor restoration in individuals with paralysis (UP2 NCT05665998). This work establishes the technological foundation required to enable the use of bidirectional neuroprosthetics in real-world conditions.

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Nanosymposium

NANO25: Value, Memory, and Social Inference: Multi-Circuit Dynamics of Human Cognition

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Time: Monday, November 16, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO25.01

Topic: I.08. Learning and Memory

Support: R00MH132873

Title: Hippocampal-cingulate dynamics in the human brain link reinforcement-learning and memory

Authors: *S. E. QASIM[1], F. PANOV[2], A. E. RHONE[3], H. KAWASAKI[4], C. K. KOVACH[5], B. J. DLOUHY[3], X. GU[6], I. SAEZ[7];
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Abstract: Reward-prediction errors (RPEs) influence adaptive decision-making, but growing evidence suggests they also enhance memory for events encountered during learning. The circuit-level mechanisms linking reinforcement learning computations to episodic memory in humans remain unclear. Here, we combined computational modeling with intracranial electrophysiology in epilepsy patients performing a probabilistic reversal-learning task followed by recognition memory. During learning, each reward outcome was paired with a trial-unique image stimulus. Reinforcement-learning models revealed that positive RPEs predicted subsequent memory for associated images in both healthy controls and neurosurgical patients. Intracranial recordings demonstrated that multivariate high-frequency activity encoded RPE information broadly across prefrontal cortex during reward feedback, including orbitofrontal, anterior cingulate, and dorsomedial prefrontal cortex. During subsequent recognition, however, only anterior cingulate cortex (ACC) reactivated feedback-related RPE representations. This reactivation emerged approximately 300-640 ms following cue onset and coincided with ACC decoding of upcoming memory decisions for previously encountered images. Representational similarity analyses further revealed that successful recognition was associated not with local ACC reinstatement alone, but with hippocampal reinstatement of ACC feedback representations. Hippocampal theta activity decoded successful recognition and exhibited increased directed theta synchrony toward ACC during recognition of stimuli previously associated with positive RPEs. Across participants, hippocampus-to-ACC theta synchrony predicted both hippocampal memory decoding and ACC RPE reactivation strength. These findings identify a hippocampal-cingulate mechanism through which reinforcement-learning computations influence episodic memory, linking value-based learning signals to selective memory persistence in the human brain.

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Nanosymposium

NANO25: Value, Memory, and Social Inference: Multi-Circuit Dynamics of Human Cognition

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Topic: I.08. Learning and Memory

Support: Lundbeck Foundation R368-2021-325
Lundbeck Foundation R483-2024-1606

Title: Sub-second dopamine dynamics in human thalamus during risky behaviour

Authors: W. LIN[1], ***D. BANG**[1,2];
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Abstract: Striking the right balance between risky and safe choices is critical for adaptive behaviour. Indeed, risk preferences are emerging as a promising neuropsychiatric marker of healthy function. For example, risk aversion is elevated in anxiety and depression, whereas extreme risk-seeking is apparent in problem gambling. Animal research has long implicated dopamine (DA) in risk-related processes, and drugs that target the DA system in humans have been shown to affect risky behaviour. However, direct human evidence is lacking. Here, we address this gap by using fast scan cyclic voltammetry (FSCV) to record sub-second (10 Hz) DA fluctuations in the human thalamus - a key DA projection target in the primate brain - in essential tremor and Parkinson's disease patients undergoing awake deep brain stimulation surgery. During the recordings, the patients performed a reinforcement learning task in which they, on each trial, had to draw a card from one of two decks, which differed in their means and/or variances within each block of trials. The trial outcome depended on the difference in value between the cards drawn from the chosen and unchosen decks, which were revealed sequentially in random order. When faced with decks with similar means, the proportion of trials in which an individual draws from the more variable deck provided a metric of their risk preference (low: risk averse; high: risk seeking). Using a reinforcement learning model, we found that DA tracked reward prediction errors (RPEs) - the difference between the received and expected outcome - and that the strength of this response predicted an individual's tendency to draw from the more variable deck. Indicative of a temporal difference RPE, DA increased/decreased with changes in the expected outcome during the sequential reveal of the chosen and unchosen options. Our results provide direct human evidence for a role of DA in shaping risk preferences.

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Title: Working memory fails when prefrontal subspace geometry collapses under load

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Abstract: Working memory (WM) relies on the brain's ability to transform transient sensory input into persistent internal neural states. Although the prefrontal cortex (PFC) has long been implicated in WM maintenance, it remains unclear how human PFC population activity sustains mnemonic representations, or why these representations fail when demands exceed capacity. Recent work suggests that behaviorally relevant computations are organized within low-dimensional subspaces that structure neural population activity. Here, we show that such subspaces also structure human PFC population activity during WM maintenance. We recorded intracranial electroencephalography (iEEG) from 14 pharmacoresistant epilepsy patients while they performed a WM task and a perceptually-matched control task without memory. In the WM task, participants maintained 1, 3, or 5 locations across a delay, whereas in the control task, the same arrays and fully valid spatial cues guided probe responses without requiring memory maintenance. Increasing load selectively impaired WM, as reaction times increased more across load than in the control task ($P = 0.0006$), and accuracy declined with load ($P = 0.0008$). This behavioral cost was reflected in the geometry of PFC population activity. Mapping trial-by-trial PFC activity into low-dimensional subspaces revealed that the two tasks exhibited similar dimensionality during sensory processing but diverged during maintenance, when WM activity expanded into higher-dimensional patterns ($P = 0.0277$). Lower-dimensional modes were largely shared across tasks, whereas higher-dimensional modes displayed task-specific dynamics. Critically, during the delay, single-trial PFC activity became less dispersed within the working-memory subspace under high memory load ($P = 0.0256$), indicating a collapse of the PFC representational geometry supporting successful maintenance. Across participants, this subspace collapse tracked the decline in working-memory accuracy ($r = 0.76$, $P = 0.002$), linking PFC population geometry to behavioral capacity limits. In sum, these findings reveal dynamic reconfiguration of human PFC population activity during working memory and identify PFC representational collapse under high load as a neural signature of capacity limits.

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Title: Network and cellular dynamics underlying mental manipulation of object sequences

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Abstract: The ability to manipulate information in mind is a defining feature of human cognition, but the neuronal mechanisms that enable this capacity remain unclear. We leveraged the high spatiotemporal fidelity of human intracranial recordings to examine how the brain transforms mentally held object sequences. In an auditory working memory task (N = 30), mental manipulation evoked an increase in medial-temporal (MTL) lower-frequency dynamics

and enhanced directed theta-alpha synchrony (6-10 Hz), especially between auditory, prefrontal, and hippocampal areas. The strength of this coupling predicted imagery vividness and task performance. In parallel, the tonic activity of individually-recorded MTL neurons discriminated between conditions, suggesting a different excitability state during mental manipulation compared to simple recall. In a separate visual working memory experiment (N = 12), cued mental manipulation enhanced delay-period persistent firing of image-selective MTL neurons. Crucially, selective neurons tended to fire in forward sequences during simple recall and backward sequences during temporal inversion with respect to the position of their preferred image during encoding. These findings suggest that mental manipulation relies on distributed lower-frequency control dynamics and reconfiguration of neural sequences via intentional replay.

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Title: Neural geometry in the human hippocampus enables generalization across spatial position and gaze

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Abstract: Hippocampal neurons track positions of self, others, and gaze direction. However, it is unclear how their respective neural codes differ enough to avoid confusion while allowing for abstraction across spatial frames. We recorded from populations of hippocampal neurons while human participants performed a joystick-controlled virtual prey-pursuit task. We found that neurons have mixed selective responses that map positions of self, prey, and predator, as well as gaze direction. Their codes occupied mostly orthogonal subspaces, but these subspaces'

geometric structure allowed them to be aligned by simple linear transformations. Moreover, their geometry supported some degree of generalization, such that a linear rule learned on one agent transfers to another. This scheme enables reliable individuation and abstraction across both agent identity and viewpoint. Together, these findings suggest that hippocampal spatial knowledge is structured as a family of geometrically related manifolds that can be flexibly aligned across multiple maps.

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Title: Neural dynamics of one-shot perceptual learning in humans

Authors: *J. D. SHOR[1], J. S. PARK[1], D. FRIEDMAN[2], P. C. DUGAN[2], B. J. HE[3];
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Abstract: Object recognition under ambiguity requires matching the sensory input with one's prior knowledge to arrive at a best fit. Individuals vary in how strongly prior knowledge influences perception, and disturbances of this process may lead to hallucination. Distinct sources of prior knowledge have been identified to influence recognition, including past experiences and top-down expectation. Here, we investigate neural network dynamics underlying past experiences' influence on perception using intracranial EEG (iEEG) and a dramatic one-shot perceptual learning task. Prior studies have shown that multiple large-scale cortical networks are involved in prior-knowledge-guided perceptual recognition. Notably, a recent study in brain-lesioned patients showed that the hippocampus and related medial temporal lobe structures are not needed for successful one-shot perceptual learning. This finding confirms that cortical networks implement prior-knowledge-guided perceptual recognition; however, the involved network dynamics remain largely unknown. In this study, we leveraged the high spatial and temporal resolution of (iEEG) to examine the timing properties of neural activity changes induced by one-shot perceptual learning in multiple cortical networks to better understand the involved mechanisms. Patients undergoing surgical evaluation with iEEG monitoring are shown degraded black-and-white images and asked if they can recognize a coherent object in the image. By presenting a degraded image both before (pre-) and after (post-) its corresponding original

grayscale image (which induces disambiguation of the degraded image), the distinct neural activity of prior-knowledge-induced recognition can be discerned. We measured the neural activity, as indexed by high gamma (50-120 Hz) power, and found distinct activity for both unrecognized pre- and recognized post- presentations in visual cortex as well as the default mode network and frontoparietal network, demonstrating the widespread impact of prior-knowledge availability. Further analyses measured the shift in neural representations during degraded image viewing to become more aligned with representations during the disambiguating grayscale images, and only found this shift towards the prior-knowledge in visual cortex. We detected this shift first in the high-order visual cortex (HLVC) of the ventral stream as rapidly as 250 ms after image onset. A later shift in early visual cortex regions may indicate top-down feedback from HLVC. We find HLVC is the most parsimonious site for the plasticity needed to support the one-shot perceptual learning exhibited in this task.

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Title: Anterior Insula Causally Links Threat Processing to Pupil-Indexed Arousal During Human Approach-Avoidance Conflict

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Abstract: Approach-avoidance conflict requires balancing reward seeking against potential threat and is a core feature of adaptive behavior and anxiety-related disorders. Although autonomic arousal is known to influence decision-making during threat, the neural circuits linking threat processing to autonomic state changes in humans remain poorly understood. Here, we combined intracranial electrophysiological recordings, pupillometry, and causal lesion data to investigate the neural mechanisms underlying autonomic arousal during approach-avoidance conflict.
Twenty-five neurosurgical patients performed a dynamic approach-avoidance task in which participants collected rewards while avoiding pursuit and attack by a virtual predator. Simultaneous eye tracking was used to quantify pupil diameter as an index of autonomic arousal. High-frequency activity (70-170 Hz) was extracted from intracranial recordings across cortical and subcortical regions. To assess causal contributions, a subset of participants completed the task both before and after radiofrequency ablation, including five patients with unilateral amygdala ablation and one patient with right anterior insula ablation.
Threat pursuit and attack elicited robust increases in pupil diameter compared with foraging periods. Across participants, high-frequency activity in the anterior insula and ventral thalamic regions significantly predicted trial-by-trial pupil dilation during threat encounters. Critically, the participant who underwent right anterior insula ablation exhibited a marked reduction in threat-evoked pupil dilation following ablation, providing causal evidence that the anterior insula contributes to autonomic arousal during approach-avoidance conflict. In contrast, unilateral amygdala ablation did not produce consistent changes in pupil responses or task behavior.
These findings identify the anterior insula as a key node linking threat processing to autonomic state changes in humans and suggest that pupil-linked arousal during defensive behavior is more closely associated with insular and thalamic circuits than with amygdala activity. By integrating intracranial recordings with causal perturbation, this study provides new insight into the neural mechanisms that transform threat into autonomic and behavioral responses during approach-avoidance conflict.

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Title: Cortical-limbic circuit dynamics of approach-avoidance conflict in humans

Authors: *B. R. STAVELAND[1], B. BERGER[2], T. MINARIK[3], O. KIM-MCMANUS[6], J. T. WILLIE[7], P. BRUNNER[8], M. DASTJERDI[9], J. J. LIN[10], E. JOHNSON[11], M. R. PAFF[12], M. HSU[4], R. T. KNIGHT[5];
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Abstract: Choosing to approach or avoid is common in everyday life, and excessive avoidance is a cardinal feature of anxiety disorders. Identifying the human neural circuits mediating this behavior may reveal therapeutic targets for circuit-based interventions. Here we use intracranial EEG to define a prefrontal-limbic circuit supporting approach and avoidance. Presurgical epilepsy patients (n = 20) performed an approach-avoidance conflict task inspired by Pac-Man, trading off rewards against losses from ghost attack. During approach, theta power increases across a limbic circuit including the hippocampus, amygdala, orbitofrontal cortex and anterior cingulate cortex, and drops during avoidance (Hippocampus Conflict-Trial $Estimate_{approach>avoidance}$: 0.24, 95% CI [0.10-0.37], $P_+ > 0.99$, $BF_{10} > 4$, ESSbulk = 3838.9, Ratio of Sig. $Electrodes_{P+} > 0.95$ = 72/115), Amygdala Conflict-Trial $Estimate_{approach>avoidance}$: 0.16, 95% CI [0.07-0.26], $P_+ > 0.99$, $BF_{10} > 3$, ESSbulk = 5903.8, Ratio of Sig. $Electrodes_{P+} > 0.95$ = 59/101, OFC Conflict-Trial $Estimate_{approach>avoidance}$: 0.21, 95% CI [0.13-0.29], $P_+ > 0.99$, $BF_{10} > 100$, ESSbulk = 4243.2, Ratio of Sig. $Electrodes_{P+} > 0.95$ = 127/167) and ACC Conflict-Trial $Estimate_{approach>avoidance}$: 0.26, 95% CI [0.14-0.38], $P_+ > 0.99$, $BF_{10} > 18$, ESSbulk = 7222.9, Ratio of Sig. $Electrodes_{P+} > 0.95$ = 50/73). Theta connectivity between this circuit and lateral prefrontal cortex tracks approach duration, with enhanced synchrony extending approach times (Estimate: 0.09, 95% CI [0.05-0.14], $P_+ > 0.99$, $BF_{10} > 9$, ESSbulk = 7680.4, Ratio of Sig. $Electrodes_{P+}+ > 0.95$ = 1782/2816). Under imminent threat, the system switches to sustained high-frequency activity in the lateral prefrontal cortex. Finally, oscillations in the insula may signal this switch from ambiguous to imminent threat. Together, these findings characterize a distributed human circuit underlying approach-avoidance conflict with implications for understanding and targeting maladaptive avoidance in anxiety.

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Title: Neural signatures of impaired semantic contextualization in Autism Spectrum Disorder

Authors: *M. FRANCH[1], K. KATLOWITZ[1], E. MICKIEWICZ[1], J. BELANGER[2], R. MATHURA[1], H. ZHU[1], X. YAN[3], N. R. PROVENZA[4], S. A. SHETH[4], B. Y. HAYDEN[1]; [1]Baylor Col. of Med., Houston, TX; [2]Baylor Col. of Med., Sugar Land, TX; [3]Dept. of Neurosurg., [4]Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Social and communicative deficits are defining characteristics of autism spectrum disorder (ASD). Some theories suggest that these challenges, among other autistic traits, may arise from differences in predictive coding, or how the brain uses context to predict and interpret incoming information. This idea has the potential to link symptoms of autism to specific neurocomputational processes, and is especially promising for communication, whose impairment is a hallmark of ASD. Here we leveraged the ability of large language models (LLMs) to quantify semantic contextualization to analyze a unique dataset of responses from hippocampal neurons obtained during language listening in three mild-to-severe autistic individuals with comorbid epilepsy. Key elements of semantic coding were preserved in all three individuals with ASD: single-neuron response dynamics, representation of word-word semantic relationships, and patterns of context-dependent shifts in meaning. However, relative to controls, ASD resulted in reduced neural signatures of contextualization: (1) neuronal responses were aligned with earlier, less contextual layers of GPT-2, (2) ASD patients had lower effective dimensionality of the neural subspace predicting semantics, (3) neural representations of word meaning were less influenced by preceding context, and (4) neural signatures of lexical surprisal were reduced. Together, these results support theories of autism that emphasize impairments in contextualization, and highlight the power of LLMs as a tool for quantifying the computational basis of neurodevelopmental disorders.

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Title: Distinct Neural Encoding of Past, Present, and Future During Natural Conversations: An ECoG Study

Authors: *I. JALON[1], H. WANG[2], Z. ZADA[2], B. AUBREY[3], A. BHATTACHARJEE[3], S. A. NASTASE[3], A. Y. GOLDSTEIN[4], O. DEVINSKY[5], A. FLINKER[6], U. HASSON[7];
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Abstract: Engaging in natural conversation is a complex cognitive task that requires processing current words while maintaining a dynamic mental representation of previously spoken words in context and planning and predicting future utterances. The underlying neural processes of spontaneous speech planning and prediction are often implicit and difficult to study. We utilize intracranial electrocorticography (ECoG) to investigate how the brain encodes past and future temporal features during the generation of words in natural conversation. Brain encoding models were trained to predict ECoG signals from 100 hours of continuous speech recordings during natural conversations, utilizing context-aware language embeddings. Grouped ridge regression models were constructed using three temporal context feature groups: current word, recent past (8 words), and the upcoming future (8 words). These linguistic features were mapped to ECoG signals. Models were evaluated using cross-validation within four patients. Analyses were performed separately for production and comprehension and evaluated on a minimum of 35,000 samples per model. Our models revealed spatiotemporally distinct neural encoding of past, present, and future contexts. The representation of the present word was transient and localized, decaying rapidly within 150 ms, and was encoded more strongly during production than comprehension. In contrast, past and future representations were stable, with decay times exceeding 20s. We identified electrodes selectively tuned to the past, future, or both, during both production and comprehension. Planning signals for upcoming sentences were identifiable in IFG, while the conversational past was more richly represented during comprehension. Form and meaning made regionally distinct contributions to these representations. For example, during

production, motor cortex was selective for form and the middle temporal gyrus for meaning while other regions showed equal sensitivity. These findings demonstrate that context-aware encoding models successfully dissociate the neural representations of conversational past and future from the present. This spatiotemporal organization, consisting of transient encoding of the current word alongside sustained signals that maintain prior context and support the planning of upcoming speech, offers a finer-grained understanding of the cognitive processes underlying natural conversations.

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Title: A sensory-to-social cascade in face perception is reorganized in autism

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Abstract: First impressions arise within fractions of a second from viewing a face, requiring a rapid transformation from visual representations of facial features to abstract social evaluations. How this sensory-to-social transformation unfolds across the human brain, and how it is altered in conditions of atypical social cognition, remains poorly understood. Using intracranial EEG (iEEG) recordings from 31 neurotypical individuals, we characterized the spatiotemporal dynamics of this transformation during face viewing. Time-resolved partial representational similarity analysis revealed a dynamic propagation cascade in which visual feature representations emerged rapidly and broadly across the face-processing network, including higher-order social-evaluative regions. Over time, this initially distributed representation differentiated into a hierarchical organization, with visual feature encoding remaining strongest in posterior regions while social trait representations increasingly dominated higher-order social-evaluative. Directional connectivity analyses further indicated that information flow along this cascade was predominantly feedforward from the fusiform gyrus (FG). In two individuals with autism spectrum disorder (ASD), iEEG recordings revealed a reorganized cascade characterized by reduced posterior face processing, enhanced encoding of visual facial features in frontal regions, and strengthened feedforward propagation. An independent fMRI cohort (25 ASD, 25 neurotypical participants) confirmed this spatial reorganization at the group level, showing reduced posterior and increased frontal responses, as well as enhanced FG-frontal connectivity during face processing in ASD. Together, these findings identify sensory-to-social propagation as a fundamental organizing principle of face-based social inference and suggest that this process is redistributed in ASD, with diminished engagement of specialized sensory regions accompanied by compensatory frontal recruitment. More broadly, the results provide a mechanistic framework for understanding how facial appearance is transformed into social meaning and how this transformation is altered in atypical social cognition.

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Nanosymposium

NANO25: Value, Memory, and Social Inference: Multi-Circuit Dynamics of Human Cognition

Location: WCC Rm 143

Time: Monday, November 16, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO25.12

Topic: I.08. Learning and Memory

Title: Shared neural dynamics underpin social belief inference

Authors: *S. A. RHOADS[1], S. E. QASIM[2], F. PANOV[1], L. NUNEZ MARTINEZ[1], W. YOSHIDA[3], M. HO[4], I. SAEZ[1], X. GU[1];
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Abstract: Humans infer and predict others' internal states with remarkable accuracy—an ability crucial for successful coordination. Yet the neural dynamics supporting accurate social inference are poorly understood. We simultaneously recorded intracranial local field potentials from human dyads while they completed a cooperative turn-based game (14 subjects; 8 unique dyads; 192 games; 409 electrodes). A theory-of-mind computational model quantified, on each turn, how deeply an observer inferred an actor's strategy (recursive reasoning depth), the uncertainty in that belief, and whether an observer's inferred strategy aligned with an actor's strategy (belief alignment). Low-frequency activity in dorsomedial prefrontal cortex and superior temporal sulcus tracked recursive reasoning depth (FWE $p<.05$), and low-frequency activity in anterior cingulate tracked belief uncertainty (FWE $p<.05$). Higher belief alignment between observers and actors was linked to increased interbrain mutual information in several brain regions, including the superior temporal sulcus (FWE $p<.05$), reflecting neurophysiological signatures supporting the alignment of abstract representations between partners. Together, these results provide a neurophysiological and computational account of how abstract beliefs about others are aligned across brains to support cooperative planning.

Disclosures: S.A. Rhoads: None. **S.E. Qasim:** None. **F. panov:** None. **L. Nunez Martinez:** None. **W. Yoshida:** None. **M. Ho:** None. **I. Saez:** None. **X. Gu:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.01

Topic: A.08. Adolescent Development

Support: National Natural Science Foundation of China U20A20221
National Natural Science Foundation of China 819611280292
National Natural Science Foundation of China 82501864
Nathan Kline Institute Pilot Grant

Title: Development of brainwide cortical functional connectivity from amygdala in juvenile macaques revealed by INS-fMRI

Authors: *Y. FENG[1,2], F. TIAN[1], A. PING[1], M. QIAN[3], J. WANG[1], A. W. ROE[3,4]; [1]Zhejiang Univ., Hangzhou, China; [2]Columbia Univ., New York, NY; [3]Nathan Kline Inst. for Psychiatric Res., Orangeburg, NY; [4]NYU Grossman Sch. of Med., New York, NY

Abstract: Introduction: Adolescence is a critical period for cognitive and social maturation and is associated with remodeling of functional connectivity between the amygdala and prefrontal cortex (PFC). We previously demonstrated that, in adult macaques, amygdala outputs form extensive yet topographically organized mesoscale networks that contact sensory, motor, limbic and prefrontal regions in a patchy manner (Ping 2025 National Sci Rev). Here, we hypothesize that during juvenile development, influences from amygdala undergo brainwide maturation

consisting of pruning, leading to reduced and more refined connectivity, which in PFC may appear as patchy, feedback-dominated connectivity. **Methods:** We used focal infrared neural stimulation combined with ultrahigh-field 7T MRI (INS-fMRI) to map brain-wide mesoscale functional networks *in vivo* in macaque monkeys (1.5 mm isotropic resolution) (Feng 2026 Cell Reports). Three juvenile monkeys were studied longitudinally with repeated INS-fMRI measurements every six months from 2 to 4 years of age. To examine the development of laminar organization, layer-specific fMRI was additionally acquired in two monkeys using a custom 4-channel receive coil over PFC and single-shot EPI (0.35 × 0.35 × 1 mm in-plane resolution; 10-15 slices). **Results:** Longitudinal INS-fMRI following stimulation of similar sites in basal amygdala revealed a progressive reduction in brain-wide functional connectivity from 2 to 4 years of age in the same monkey (Monkey D). The decline was most pronounced in visual cortical regions, whereas connectivity with prefrontal areas (8Bd, 9, and 10o) increased. High-resolution layer fMRI provided preliminary evidence for maturation of amygdala-prefrontal circuitry. At 2 years of age, prefrontal activations were sparse and lacked clear laminar or columnar organization. By 3 years, activations became increasingly localized, exhibiting patchy columnar patterns, accompanied by a shift in activation from middle to superficial layers. **Conclusion:** These findings are consistent with initially widespread mesoscale networks which undergo refinement and activity-dependent pruning during adolescence. Local refinement during this period leads to the emergence of maturing columnar architecture and greater emphasis on cortical feedback dominance. These observations may suggest a neurodevelopmental basis for social and cognitive development in primates.

Disclosures: Y. Feng: None. **F. Tian:** None. **A. Ping:** None. **M. Qian:** None. **J. Wang:** None. **A.W. Roe:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.02

Topic: A.08. Adolescent Development

Support: Intramural Research Program of the NIMH (ZIA MH002984)

Title: Medial pulvinar input drives anatomical maturation of prefrontal neurons

Authors: *M. WALKER[1], J. JONTZ[1], A. CACCAVANO[2], K. A. PELKEY[3], J. SCOTT[5], C. J. MCBAIN[4], J. A. BOURNE[6];
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Abstract: The evolutionarily expanded primate thalamus is thought to play a critical role in shaping development of higher-order circuitry involved in cognitive function, yet its contribution to prefrontal cortex (PFC) maturation remains poorly understood. Here, we investigate the developmental influence of the medial pulvinar (PM)—a higher-order thalamic nucleus unique to primates—on the maturation of neurons in the PFC. To disrupt PM output at key developmental stages, we performed bilateral excitotoxic lesions of the PM in the common marmoset (*Callithrix jacchus*) at postnatal day 14 and in adulthood, respectively. After recovery, lesioned animals developed normally and were sacrificed in adulthood for analysis compared with unlesioned controls. Using immunohistochemistry, hybridization chain reaction, and whole-cell biocytin fills, we assessed the long-term effects of early-life PM disruption on PFC neuronal morphology and maturation state. The density of PFC parvalbumin-expressing (PV) interneurons was reduced following early-life PM lesions but not after adult-onset lesions, suggesting a critical developmental window for thalamic influence. Prefrontal PV interneurons from early-life lesioned animals also exhibited smaller soma, had less complex axonal arborizations, and expressed fewer transcripts for the PGC-1α gene, which encodes a transcriptional coactivator known to drive molecular maturation of PV INs. Similarly, layer III pyramidal neurons in the early-life lesioned marmosets were reduced in size in the PFC but not in the primary motor cortex, indicating specificity for cortical areas connected to the PM. These findings demonstrate that developmental input from the PM is necessary for normal maturation of prefrontal neurons, especially PV interneurons. This work identifies a primate-specific thalamocortical pathway that shapes PFC development and highlights a potential developmental vulnerability relevant to neurodevelopmental disorders such as schizophrenia.

Disclosures: M. Walker: None. **J. Jontz:** None. **A. Caccavano:** None. **K.A. Pelkey:** None. **J. Scott:** None. **C.J. McBain:** None. **J.A. Bourne:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.03

Topic: A.08. Adolescent Development

Support: CIHR

Title: Activity-dependent myelination in prefrontal circuits signals the offset of infantile amnesia

Authors: *A. GOLBABAEI[1], S. A. JOSSELYN[2], P. W. FRANKLAND[3];
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Abstract: Human and non-human infants can form memories for events, but these memories are not successfully consolidated into remote memory. While the neurobiological basis of this phenomenon—known as infantile amnesia—remains unclear, it is hypothesized that the neural

circuits required for successful consolidation are insufficiently mature. Here we find that heightened activity in the prelimbic cortex of developing mice triggers a sequalae of maturational steps that culminates in adult-like memory persistence: Activity-dependent increases in brain-derived neurotrophic factor (BDNF) promote myelination of prelimbic circuits via activation of tyrosine kinase receptor B (TrkB) receptors on oligodendrocyte precursor cells (OPCs). Inhibiting any of these steps within a critical developmental window delays the offset of infantile amnesia, whereas promoting this sequalae results in the precocial emergence of memory persistence. Similar to critical periods in sensory cortices, our results indicate that developmental myelination is required for proper circuit maturation and emergence of adult-like memory function.

Disclosures: A. Golbabaei: None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.04

Topic: A.08. Adolescent Development

Support: DUCOM Deans' Fellowship 2024 to LTF
NIH/NIMH R21MH129989
R01MH131053
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Title: Investigating the effects of adolescent social isolation and psilocybin exposure

Authors: *L. FLYNN[1], W.-J. GAO[2];
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Abstract: Increasingly, psychedelic compounds (e.g., psilocybin) are being used for the treatment of neuropsychiatric conditions, owing in large part to their rapid onset and sustained duration of effects. While the mechanisms of action underlying psychedelic therapeutic effects are not entirely known, research supports the role of psychedelic-induced increases in synaptic plasticity in key brain regions, including the prefrontal cortex (PFC). Adolescence is a critical period for the onset of most neuropsychiatric and substance abuse disorders, and the PFC experiences extensive neural plasticity and gradual maturation during this developmental period. While recreational use of psychedelic compounds during adolescence has been established in the literature, and adolescent onset of psychiatric disease has caused some researchers and clinicians to suggest the use of psychedelic therapy in adolescence, the effects of adolescent psychedelic exposure are almost entirely unknown. Most preclinical studies are conducted in adult animals, and the safety profile of these compounds in adolescence has not been investigated. Furthermore, the long-term effects of adolescent psychedelic exposure are almost entirely unexplored. Here, we aimed to investigate the short- and long-term behavioral, electrophysiological, and epigenetic

effects of adolescent psychedelic exposure in both healthy animals and animals exposed to adolescent social isolation. To this end, we first administered the classic serotonergic psychedelic psilocybin or saline to male and female adolescent (P28) C57BL/6J mice and twenty-four hours or four weeks after drug administration, animals underwent assessment of social (three-chamber test of social preference), anxiety-like (open field test), and depressive-like (tail suspension test) behavior. In a separate group of animals, psilocybin or saline was administered at P28 and twenty-four hours or four weeks later, animals were sacrificed for whole-cell patch clamp electrophysiological recording of the mPFC. Finally, to investigate the ability of psilocybin to reverse adolescent social isolation-induced deficits, adolescent male and female mice underwent four weeks of group housing or social isolation followed by a single i.p. injection of psilocybin or saline. Twenty-four hours after drug administration, animals underwent behavioral assessment or sacrifice for whole-cell patch clamp electrophysiology recordings or DNA methylation assays.

Disclosures: L. Flynn: None. **W. Gao:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.05

Topic: A.08. Adolescent Development

Support: Georgetown University

Title: Prototype-Based Category Generalization in Adolescents: Evidence from Computational Modeling and Model-Based fMRI

Authors: *G. CHOE[1], G. CLAROT[1], Y. CHEN[1], D. ZEITHAMOVA[2], A. S. VANMETER[3], L. KENWORTHY[4], C. J. VAIDYA[1];
[1]Georgetown Univ., Washington, DC; [2]Psychology, Univ. of Oregon, Eugene, OR; [3]Georgetown Univ. Med. Ctr., Washington, DC; [4]Children's Natl. Hosp., Washington, DC

Abstract: Background: Generalizing knowledge to novel situations is essential for adaptive behavior. In category learning, prototype and exemplar models offer contrasting accounts of how concepts are represented, either as abstract prototypes or individual exemplars. Recent adult studies suggest category judgments are primarily prototype-based, with associated activity in the ventromedial prefrontal cortex (vmPFC) and anterior hippocampus (HPC). However, little is known about this process in development. Here, we used computational modeling and model-based fMRI to characterize individual differences in category representations and their neural basis in typically developing youth. We also examined associations with adaptive functioning. **Methods**: 35 adolescents (14-18 years; N = 30 after fMRI quality control) completed a category learning task in which they learned to categorize stimuli via feedback and generalized to old and new stimuli varying in similarity to prototypes during fMRI. Prototype and exemplar models were fit to generalization data to determine each participant's best-fitting strategy. Model-

derived variables were used to identify neural correlates of prototype and exemplar representations within a priori ROIs (vmPFC, anterior/posterior HPC) and in whole-brain analyses (voxelwise $p < .005$, cluster-corrected $p < .05$). Adaptive functioning was assessed using the Adaptive Behavior Assessment System (ABAS-3; parent report). An adult sample ($N = 41$) completed the task as a behavioral reference.
Results: Both adolescents and adults showed similar typicality gradients at test, with highest categorization accuracy for never-before-seen prototypes and stimuli most similar to prototypes ($p < .001$). Generalization accuracy showed a marginal association with ABAS across groups ($p = .053$). The prototype model fit better than the exemplar model ($p = .01$), with 80% of participants in both groups classified as prototype-dominant learners. ROI analyses revealed prototype neural correlates in vmPFC and anterior HPC, and whole-brain analyses identified additional correlates in occipital, temporal, parietal and frontal regions. Follow-up analyses showed that prototype neural correlates in the middle frontal gyrus were positively associated with ABAS ($p < .02$).
Conclusion: Category generalization in adolescents appears to be primarily prototype-based, similar to adults. Additional frontoparietal involvement not previously reported in adults may reflect developmental differences in neural mechanisms. Exploratory findings suggest that these frontoparietal contributions may play a role in adaptive functioning during adolescence.

Disclosures: G. Choe: None. **G. Clarot:** None. **Y. Chen:** None. **D. Zeithamova:** None. **A.S. VanMeter:** None. **L. Kenworthy:** None. **C.J. Vaidya:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

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Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.06

Topic: A.08. Adolescent Development

Support: U01DA055344

Title: Behavioral double dissociation across the adolescent 24-hour day: sleep trajectories track mental health, screen-time and physical-activity trajectories track cognition

Authors: *X. LI[1], W. YIN[1], T. LI[3], H. ZHU[2], W. LIN[4];
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Abstract: Screen time, physical activity, and sleep are the principal modifiable behaviors of the adolescent 24-hour day, yet their potential effects on cognition and mental health are almost always studied separately and cross-sectionally. We leveraged Adolescent Brain Cognitive Development (ABCD) Study (n=11,096) followed across five annual visits (mean age 9.9 to 14.1 years). We asked how each behavior's multi-year trajectory relates to cognition and mental

health, and whether the behaviors combine into joint phenotypes. Latent class growth analysis yielded trajectory groups (screen time, 2; physical activity, 4; sleep, 3). Groups were compared on NIH Toolbox cognition and Child Behavior Checklist (CBCL) parent-reported mental health using linear models adjusted for age, sex, and maternal education with Benjamini-Hochberg FDR correction. Considered individually, the behaviors showed a domain double dissociation. Sleep carried the largest mental-health associations: the short-declining-sleep group (n=1,042) showed elevated Total, Internalizing, Externalizing, Thought, and Attention problems (Total Problems +4.6 T-points; Thought z=12.1, -log10 FDR p > 30), while physical activity was smaller and parallel and screen time uniformly weak. The pattern reversed for cognition: the high-screen and low-activity groups scored lower on Crystallized ability, Picture Vocabulary, and Reading (-log10 FDR P > 4; screen ~3-4 and activity ~2 standard-score points lower), whereas processing speed, inhibition, and fluid composites were undifferentiated by any behavior. Considered jointly, we cross-classified the groups into 24 multimodal profiles. Every one of the five lowest-risk profiles contained the long-stable sleep group, whereas the highest-risk profiles paired short sleep with low physical activity (the largest, n=414). Risk accumulated across behaviors rather than arising from any single one. Together, adolescent 24-hour behavior trajectories carry outcome-specific information - sleep for mental health, screen time and physical activity for crystallized cognition - and the least favorable profiles arise from adverse behaviors in combination, supporting an integrated 24-hour framework for adolescent cognitive and mental-health risk.

Disclosures: X. Li: None. **W. Yin:** None. **T. Li:** None. **H. Zhu:** None. **W. Lin:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.07

Topic: A.06. Developmental Disorders

Support: NIH Grant 1K08MH139983
SYNGAP Research Fund
Simons Foundation 899599
Brain and Behavior Research Fund

Title: Distinguishable behavioral phenotypes produced by distinct Syngap1 mutations in rats

Authors: N. YOKOTA[1], E. A. MILLER[2], C. Y. LEE[1], A. CHAUDHRY[1], J. TON[1], F. NOBLE[1], K. MCCLUSKEY[1], K. STOVELL[1], S. TILL[3], P. C. KIND[3], H. WILLSEY[1], ***D. B. KASTNER**[1];
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Abstract: *SYNGAP1* is a synaptic Ras GTPase-activating protein with multiple complex cellular functions. Pathogenic variants in *SYNGAP1* are strongly associated with neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and epilepsy. However, the causal role of specific *SYNGAP1* variants for the complex disease symptomatology remains poorly understood. To investigate the functional consequences of distinct *SYNGAP1* disruptions, we performed large-scale multidimensional behavioral phenotyping across hundreds of rats from two lines containing different *Syngap1* mutations. The first mutation is a protein-truncating variant that produces haploinsufficiency. The second mutation selectively deletes the GAP domain, while leaving the other domains intact. Consistent with previous work, we find that the two *Syngap1* lines exhibited robust behavioral differences relative to wild-type controls. Furthermore, using rigorous quantitative behavioral analyses across a large number of animals, we find that the two mutations produced distinguishable behavioral profiles. Therefore, disruption of specific *Syngap1* functions leads to differential phenotypic outcomes. Across multiple behavioral measures, rats lacking the GAP domain exhibited more pronounced behavioral alterations than haploinsufficient animals. These findings demonstrate that distinct molecular disruptions within the same protein can produce separable behavioral phenotypes. Comprehensive behavioral characterization of domain-specific mutations may help define how different *SYNGAP1* functions contribute to neural and behavioral outcomes, providing insight into mechanisms underlying phenotypic heterogeneity associated with SYNGAP1-related neurodevelopmental disorders.

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Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.08

Topic: A.06. Developmental Disorders

Support: Simons Foundation #SFI-AN-AR-Pilot-00009928

Title: Nanoscale mapping of AMPA and NMDA receptor synaptic composition across three ASD mouse models reveals model-specific silent synapse phenotypes in mPFC, hippocampus, and striatum

Authors: *J. V. GOGOLA[1], N. B. KASTHURI[2];
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Abstract: Excitatory synapse dysfunction is a convergent feature of autism spectrum disorders (ASD), yet whether distinct genetic etiologies produce shared or divergent alterations in receptor composition remains unknown. Silent synapses - defined by the presence of NMDA receptors

without AMPA receptors - are considered immature synapses that are physically present but functionally inactive, and whose prevalence may differ systematically across ASD subtypes and brain regions.
We used expansion microscopy (LICONN) to image excitatory synapses at nanoscale resolution in medial prefrontal cortex (mPFC), hippocampus (CA3), and dorsal striatum of three ASD mouse models at postnatal day 28: Fmr1 knockout (JAX #003025), Shank3B heterozygous (JAX #017688), and Mecp2 knockout (JAX #003890). Synapses were identified anatomically with pan-protein label and co-labeled with antibodies against pan-AMPA (GluA1-preferring) and GluN1. For each synapse, we quantified total density, proportion AMPA-only, NMDA-only (silent), and dual-labeled (mature) relative to wildtype controls (n=2 males per genotype). Synapse sizes were quantified from pan-protein labeled punctum area, as a proxy for synaptic strength.
Preliminary data reveal model- and region-specific patterns consistent with each model's known molecular pathology. Fmr1 KO mice showed reduced AMPA-containing synapse proportion in HPC and mPFC, with a corresponding increase in silent synapses, consistent with impaired AMPAR surface trafficking downstream of FMRP loss. Shank3B heterozygotes exhibited reduced maturesynapse density most prominently in striatum, consistent with PSD scaffold disruption at corticostriatal synapses. Mecp2 KO mice showed an opposite hippocampal phenotype - increased proportion of AMPA-containing synapses - alongside reduced NMDA/AMPA synapse ratio in mPFC, consistent with region-specific dysregulation of GluA1 trafficking. Across all three models, striatal silent synapse proportion was elevated relative to controls, suggesting a region-specific vulnerability of corticostriatal circuits regardless of genetic etiology. Additionally, synapse size distributions differed across models in a region-specific manner, independent of silent synapse proportion.
These findings demonstrate that convergent ASD genetic etiologies produce divergent and region-specific alterations in excitatory synapse maturation state, detectable at nanoscale resolution. Ongoing experiments expand cohort sizes, add layer-specific analyses, and include a valproic acid rat model to assess whether environmentally-induced ASD produces analogous or distinct synaptic signatures.

Disclosures: J.V. Gogola: None. **N.B. Kasthuri:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.09

Topic: A.03. Axon and Dendrite Development

Support: AMED grant 3gm1310012
JSPS KAKENHI grant 20H03270
JSPS KAKENHI grant 25KJ2147

Title: Temporal gene regulatory networks reveal the molecular logic underlying postnatal maturation of subplate neurons

Authors: *Y. SUGITA[1,3], K. MORIYA-ITO[3], T. YONEDA[4], Y. YOSHIMURA[5], C. HANASHIMA[2], C. OHTAKA-MARUYAMA[3];
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Abstract: Subplate neurons (SpNs) are among the earliest-born neurons in the mammalian neocortex and play essential roles in early circuit formation. Although SpNs were long regarded as a largely transient population, our previous quantitative whole-cortex analysis showed that most early-born SpNs persist into adulthood as layer 6b (L6b) neurons. Additionally, compared with embryonic SpNs, L6b neurons are involved in neocortical circuits and serve as crucial network hubs. However, how surviving SpNs alter their developmental roles and acquire mature functional properties remains unclear.
Here, we investigated the molecular and electrophysiological maturation of SpN/L6b neurons during postnatal neocortical development. We applied the previously established birthdate-based long-term labeling methods to identify early-born SpNs and performed whole-cell patch-clamp recordings at two postnatal stages corresponding to immature SpNs and mature L6b-state neurons. We found that E12-born SpNs significantly matured action potentials, and that in E11-born SpNs specifically, the rise time of spontaneous excitatory postsynaptic currents and the distribution of their neurites differed. Electrophysiological and morphological analyses revealed progressive postnatal maturation of surviving SpNs, with distinct maturation trajectories among birthdate-defined subtypes.
Moreover, to identify molecular mechanisms underlying this maturation process, we analyzed the temporal expression patterns of genes linked to electrophysiological features in SpN/L6b neurons, compared with other cortical excitatory neurons, using multiple publicly available single-cell RNA-sequencing datasets. Stage-wise differential expression analysis identified genes dynamically regulated during postnatal maturation specifically in SpN/L6b neurons, including candidates related to membrane excitability and neuronal activity. We further inferred developmental stage-specific gene regulatory networks and identified candidate transcriptional regulators predicted to coordinate the postnatal maturation of SpN/L6b neurons.
Together, our results indicate that surviving SpN/L6b neurons undergo coordinated molecular and electrophysiological maturation after birth through dynamic changes in temporal gene expression, which are strictly regulated by transcriptional programs during the formation of mature neocortical circuits. These findings identify candidate transcriptional programs that may govern the functional transition of embryonic SpNs into mature L6b neurons.

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Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.10

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant NS084111
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NIH Grant NS119512

Title: Local lipid exchange at ER-PM contact sites is critical to support dendrite development

Authors: *C.-T. CHIEN, A. CHOI, M. SHELLY;
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Abstract: Neuronal dendrite development is strictly regulated by numerous signaling pathway to ensure precise spatiotemporal growth and network formation. $PI(4,5)P_2$ as a key second messenger at the plasma membrane (PM) involved in various signaling cascades, is a vital regulator for dendrite development. However, the two essential lipid intermediates for $PI(4,5)P_2$ homeostasis are spatially segregated at the PM and ER, making it challenging to instantly replenish $PI(4,5)P_2$ pools upon stimulation, especially at subcellular compartments such as dendritic branches and tips. The lipid transport protein, Nir2, was recently reported to facilitate $PI(4,5)P_2$ synthesis by selectively exchanging the essential lipids at specialized junctions, ER-PM contact sites. This allows rapid on-demand $PI(4,5)P_2$ replenishment from local lipid reservoir even in distal dendritic regions, which are far from the vesicular transport machinery. We thus hypothesize that Nir2 is critical to support dendrite development via the local regulation of $PI(4,5)P_2$ and downstream signaling at ER-PM contact sites. To examine Nir2 expression in developing neurons, we perform RT-PCR with mouse embryonic brains and detect robust Nir2 signal during the time window of early dendrite development. Knocking down Nir2 via shRNA in mouse embryos severely impacts dendrite outgrowth and branching in cortical pyramidal neurons. Nir2 KD dendrites can be rescued by overexpressing full-length Nir2, but not Nir2 mutants with disrupted lipid transport or membrane anchoring abilities. This highlights the functional relevance of Nir2 in regulating dendrite development through local lipid exchange. To investigate endogenous Nir2 localization and dynamic in neurons, we use CRISPR genome editing to label Nir2 protein with a fluorescent tag. Following BDNF-induced $PI(4,5)P_2$ depletion, endogenous Nir2 robustly responds and translocates to ER-PM contact sites as distinct puncta, suggesting the role of Nir2 in local $PI(4,5)P_2$ replenishment. To further validate, we use specific biosensors to monitor real-time lipid dynamics in neurons. Upon Nir2 KD, $PI(4,5)P_2$ recovery is significantly impaired, which also leads to the reduction in subsequent PIP_3 availability. Furthermore, our biochemical data demonstrate that Nir2 KD blunts the downstream Akt/GSK-3β signaling, which is known to mediate dendrite development and directly reflects the dysregulation of $PI(4,5)P_2$/ PIP_3 pools. Together, our study shows that neurons rely on Nir2 maintaining local $PI(4,5)P_2$ homeostasis at ER-PM contact sites to support downstream signaling propagation and dendrite development.

Disclosures: C. Chien: None. **A. Choi:** None. **M. Shelly:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.11

Topic: A.03. Axon and Dendrite Development

Title: Sensory neuron-derived TAG-1 controls motor axon guidance

Authors: *A. Z. XU[1,2], K. MEININGER[1,2], M. MCQUILLAN[1,2], A. MALLANNA[1,2], A. JAWORSKI[1,2];
[1]Dept. of Neuroscience, Brown Univ., Providence, RI; [2]Carney Inst. for Brain Science, Brown Univ., Providence, RI

Abstract: During nervous system development, spinal motor neurons (MNs) project their axons to various muscles in the body periphery. The molecular mechanisms that guide MN axons to their targets and away from inappropriate targets along the way remain incompletely understood. We previously discovered that the cell adhesion molecule TAG-1, which is expressed by developing MNs, plays multiple roles in MN development: it bundles motor axons during exit from the spinal cord, constrains MN cell bodies to the ventral horn, and guides motor axons past the dorsal root ganglia (DRGs). Accordingly, mice lacking TAG-1 exhibit defasciculated ventral roots, MN cell bodies that escape from the neural tube, and motor axons that misproject into the DRG. Interestingly, MN-specific deletion of TAG-1 fully recapitulates the ventral root expansion and MN emigration of the global knockout, but motor axon misprojection into the DRGs is reproduced with reduced severity. This suggests that TAG-1 derived from other sources contributes to motor axon guidance. Because TAG-1 is expressed both in the sensory neurons of the DRG and in MNs, we investigated the idea that DRG-derived and MN-derived TAG-1 synergize to guide motor axons past the DRGs. To this end, we developed a Tet-On gene expression system that allows temporally controlled and cell type-specific expression of TAG-1 in mice, and we validated that it can drive on-demand TAG-1 expression in select neuronal populations during development. We then used this approach to restore DRG TAG-1 expression in global *TAG-1* knockout embryos and found that this did not rescue fasciculation of motor axons in the ventral root nor prevent MNs from exiting the spinal cord, confirming that TAG-1 in MNs cell-autonomously controls axon fasciculation and cell body positioning. However, restoration of TAG-1 in DRGs significantly reduced the severity of motor axon misprojections in *TAG-1* knockout animals, indicating that DRG-derived TAG-1 can non-cell-autonomously guide motor axons. Our results support a non-canonical model for TAG-1 function in motor axon guidance, in which MN- and sensory neuron-derived TAG-1 cooperatively and semi-redundantly prevent motor axons from entering the DRGs.

Disclosures: A.Z. Xu: None. **K. Meininger:** None. **M. McQuillan:** None. **A. Mallanna:** None. **A. Jaworski:** None.

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.12

Topic: A.03. Axon and Dendrite Development

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R01EB035160
R01MH133836

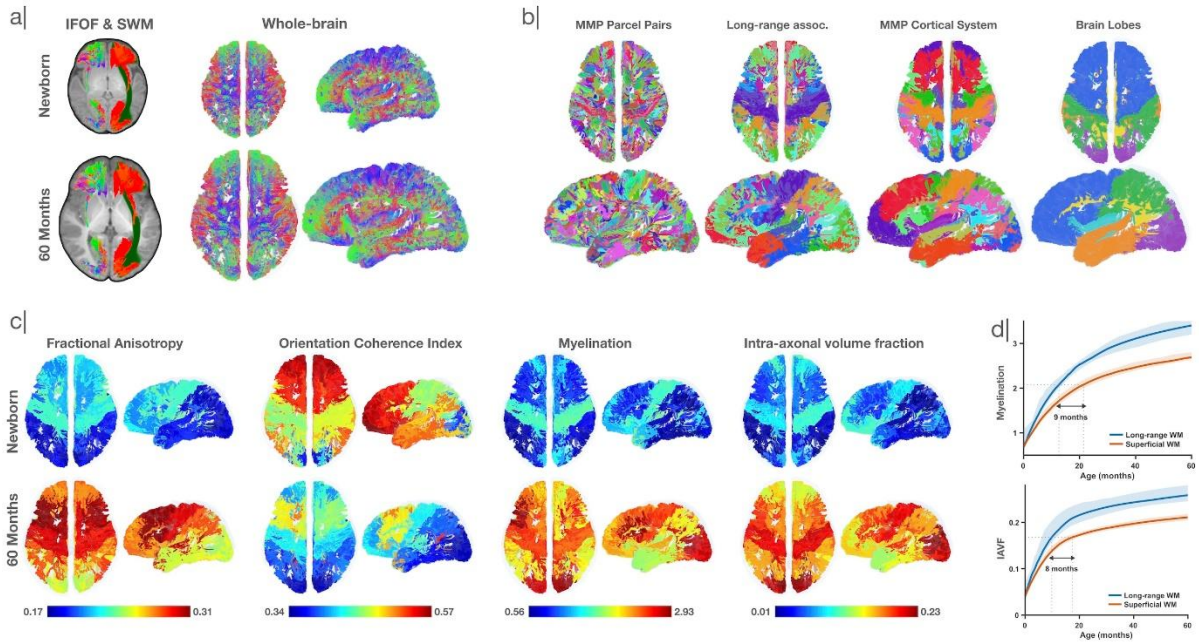
Title: Superficial white matter maturation in early childhood

Authors: *K. HUYNH[1], S. AHMAD[2], P.-T. YAP[3];
[1]Radiology, Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Dept. of Radiology and BRIC, The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Radiology, Univ. of North Carolina, Chapel Hill, NC

Abstract: The short association fibers in the superficial white matter (SWM) support most cortico-cortical communication, yet they are difficult to reconstruct and remain largely uncharted in infancy. Using surface-guided tractography, we built a continuous SWM atlas from 423 diffusion MRI scans (6-1991 days) from the Baby Connectome Project and modeled microstructural development using generalized additive mixed models across 94 SWM bundles, each anchored to its nearest deep long-range tract.

Over the first five years of life, the SWM undergoes marked growth: median intra-axonal volume fraction (IAVF) increases by 405%, myelination by 298%, and fractional anisotropy (FA) by 61%, while fiber coherence (OCI) decreases by 10%. Age effects show a similar pattern, with the strongest changes in myelin and IAVF (~0.90), and more modest changes in FA (~0.4) and OCI (~0.1), suggesting that microstructural substrate continues to build while overall coherence is largely established early.

Development follows two principal spatial gradients. FA and coherence are highest anteriorly and lowest posteriorly, whereas myelin and IAVF peak in primary sensory regions (visual and sensorimotor cortex) and are lowest in higher-order association cortex (frontal and temporal). Finally, SWM maturation lags behind adjacent deep white matter: SWM reaches a given degree of myelination about 9 months later than its corresponding long-range tract (median +8.7 months; 97% of bundle pairs), with similar delays for ICVF (~8 months) and FA (~20 months). Together, this continuous, age-resolved atlas provides a normative reference for early cortico-cortical connectivity, a system that has been largely overlooked in early brain development.



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

Nanosymposium

NANO26: Adolescent Development: Animal Models

Location: WCC Rm 207A

Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO26.13

Topic: A.03. Axon and Dendrite Development

Title: Multiscale mapping of Glial subtypes and spatial organization in the developing mouse visual system

Authors: *A. LEO JUSTIN[1], J. V. GOGOLA[2], N. B. KASTHURI[1], G. WILDENBERG[3]; [1]Neurobio., [2]Psychology, Univ. of Chicago, Chicago, IL; [3]Neurobio., Univ. of Chicago Dept. of Neurobio., Chicago, IL

Abstract: The role of glial cells and the molecular mechanisms governing retinal ganglion cell (RGC) organization have been incompletely described in literature. A key limitation in the field is the scarcity of high-resolution models that capture developing RGC axons in the process of axon pathfinding. Comprehensive 3D nanoscale maps that detail in vivo interactions between axon growth cones and guidepost cells would reveal, for the first time, how axons navigate towards their eventual targets and the actual makeup of the cellular environment they are navigating through.
We have applied two 3D nanoscale techniques to address this gap: large volume serial electron microscopy (“connectomics” or “vEM”) and expansion microscopy (ExM). vEM is used to examine the complete cellular environment of the embryonic optic nerve (ON) and optic chiasm

(OC) at E13.5; an age when early populations of RGC axons begin to enter the OC and make decisions about ipsi- versus contralateral migration. We have preliminary data from the first-ever vEM reconstruction, where we show developing RGC axons as they migrate from the optic disc in E13.5 mice.
In parallel, ExM collected across E10 to E15 timepoints in C57BL/6 female and male mixed mice to molecularly label growth cones and guidepost cells. We demonstrated ExM techniques for embryonic mice at E10 time point that capture nanoscale interactions between the two. The data combined provide the first glimpses into how axons navigate their world to faithfully find their targets and reveal new insight into the problem of axon pathfinding. We aim to quantify the distribution of developing RGC axons and to develop analytical frameworks for assessing their spatial relationships. This work will generate comprehensive vEM and ExM datasets of the ON/OC system, supported by AI-assisted segmentation and human validation. Resolving the cellular interactions that shape guidepost-mediated axon guidance at the optic chiasm is essential for understanding the developmental mechanisms underlying the formation of the binocular visual system.

Disclosures: A. leo justin: None. **J.V. Gogola:** None. **N.B. Kasthuri:** None. **G. Wildenberg:** None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO27.01

Topic: B.04. Synaptic Transmission

Support: NIH Grant R01NS134128
NIH Grant R01MH070727
NIH Grant R01MH081060
NIH Grant T32GM152284

Title: Single-synapse imaging reveals mechanistically distinct spatiotemporal properties of asynchronous neurotransmission

Authors: *K. ZHANG, L. M. MONTEGGIA, E. T. KAVALALI;
VANDERBILT UNIVERSITY, Nashville, TN

Abstract: Asynchronous neurotransmitter release extends synaptic signaling beyond the millisecond timescale of synchronous fusion and has emerged as a mechanistically distinct mode of neurotransmission implicated in circuit oscillations, synaptic plasticity, and neuropsychiatric disease. Although several manipulations are widely used to enhance excitatory asynchronous release, it remains unclear whether these conditions produce equivalent forms of delayed neurotransmission at individual synapses. In particular, the spatial organization of asynchronous neurotransmission remains poorly understood because conventional electrophysiological

approaches lack sufficient spatial resolution to resolve individual release events.
Here, we combined quantal iGluSnFR3 imaging with pixel-by-pixel temporal deconvolution to directly visualize asynchronous glutamate release at single hippocampal synapses in cultured rat neurons. We systematically tested several established paradigms that enhance asynchronous release. Although electrophysiological measurements suggested broadly similar increases in asynchronous neurotransmission across conditions, optical quantal analysis revealed distinct release phenotypes that were obscured at the population level. Different manipulations produced separable effects on the kinetic properties, quantal organization, and spatial distribution of asynchronous release events within individual active zones. Furthermore, several asynchronous phenotypes depended on synaptotagmin-7 (Syt7), supporting a selective role for Syt7 in specific forms of delayed neurotransmission.
Together, these findings demonstrate that asynchronous release is not a unitary process but instead comprises mechanistically distinct modes of neurotransmission with unique kinetic and spatial signatures at single synapses. These results provide new mechanistic insight into how distinct molecular and physiological pathways differentially organize asynchronous neurotransmission and suggest that the functional consequences of asynchronous release may depend critically on how this mode of signaling is engaged.

Disclosures: K. Zhang: None. **L.M. Monteggia:** None. **E.T. Kavalali:** None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO27.02

Topic: B.04. Synaptic Transmission

Support: ERC grant MemLessInterface – 101078172
Horizons Europe MSCA DN Grant (101167843 - BICEPS)

Title: Phase separation in synaptic homeostasis and disease

Authors: *D. MILOVANOVIC;
Inst. of Biochemistry, Charité - Berlin Univ. of Med., Berlin, Germany

Abstract: Compartmentalization of cellular processes into membrane-bound and membrane-less organelles is vital for cell function, enabling precise regulation of signaling, trafficking, and homeostasis. Recent discoveries have revealed the dynamic interplay between biomolecular condensates and membranes, highlighting their crucial role in coordinating cellular activities such as neurotransmitter release. We investigate the condensate-membrane interaction at the synapse using two condensate-forming proteins: synapsin-1, the most abundant soluble neuronal protein essential for clustering of synaptic vesicles, and PDZD8, an ER-resident proteins critical for the formation of membrane contacts between ER and mitochondria. Our data indicate that lipid composition determines the level of interaction between both synapsin-1 and PDZD8

condensates with membranes. Moreover, we established 2D graphene sensors for characterizing electric properties of these condensates and discovered that condensates accumulate electric potential at their interfaces, suggesting the biomolecular condensates as the putative mesoscale capacitors. Nowhere is this dependance more relevant than in the context of neuronal synapses where activity-dependent depolarization leads to transient ion fluxes. Our cellular models and electrical sensors will help dissect how the changing environmental conditions impact the condensate-membrane signaling cascade.

Disclosures: D. Milovanovic: None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO27.03

Topic: B.04. Synaptic Transmission

Support: NS112390
NS089578
American Parkinson's Disease Association
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Title: Synaptojanin1 regulates synaptic dopamine release and axonal integrity via retromer-dependent endosomal sorting

Authors: *P.-Y. PAN;
Rutgers Univ. Robert Wood Johnson Med. Sch., Piscataway, NJ

Abstract: Synaptic dysfunction is increasingly recognized as an early feature of Parkinson’s disease (PD); however, synaptic mechanisms contributing to early dopamine release defects and neurodegeneration remains poorly understood. Here we identify a presynaptic endosomal-dependent mechanism supporting dopamine release and axonal integrity. Loss of the PD-associated lipid enzyme Synaptojanin1 impairs dopamine release due to endosomal retention of the dopamine D2 autoreceptor and dopamine transporter. Conditional deletion of Synaptojanin1 in mouse dopamine neurons results in endosomal swelling within striatal dopamine transporter clusters and PD-like locomotor deficits. Mechanistically, Synaptojanin1 remodels endosomal phosphatidylinositol 4-phosphate to facilitate the recruitment of the PD-associated retromer component VPS35. Notably, overexpressing VPS35 rescues presynaptic sorting defects in Synaptojanin1 deficient dopamine neurons despite lipid impairments. Furthermore, Synaptojanin1 and VPS35 exhibit correlated expression and dopamine-induced co-clustering in axons, supporting their broader roles in regulating synaptic surface proteins. Our work

demonstrates a lipid-dependent endosomal mechanism that may contribute to motor deficits in early PD.

Disclosures: P. Pan: None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

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Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO27.04

Topic: B.04. Synaptic Transmission

Support: NIH/NIA K25AG086674-02

Title: BLIMPS: Multidimensional Imaging of Presynaptic Dynamics Reveals Cell-Type- and APOE4-Dependent Alterations in Hippocampal Circuits

Authors: *M. C. POTCOAVA[1], Z. ZURAWSKI[2], I. LU[3], L. M. TAI[2], S. T. ALFORD[4]; [1]Univ. of Illinois,Chicago, Chicago, IL; [2]Anat. and Cell Biol., [3]Univ. of Illinois at Chicago, Chicago, IL; [4]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL

Abstract: Balanced excitatory and inhibitory neurotransmission is essential for normal circuit function, yet monitoring presynaptic activity across genetically defined neuronal populations is technically challenging. Existing imaging approaches are limited by tradeoffs among acquisition speed, imaging depth, spatial resolution, and spectral separation. To address these limitations, we developed Biosensor Lattice Light-sheet Imaging of Multidimensional Presynaptic Structures (BLIMPS), a platform that combines lattice light-sheet microscopy with genetically encoded sensors to quantify synaptic responses during evoked release. In intact tissue in situ. We use calcium sensors to quantify presynaptic calcium dynamics in acute hippocampal slices at high spatiotemporal resolution.

We used viral expression of the calcium sensors jGCaMP8f and jRGECO1a in genetically defined neuronal populations, enabling sequential imaging of excitatory CaMKII-positive pyramidal neurons and inhibitory mDLX-positive interneurons with minimal spectral crosstalk. Acute brain slices are imaged in a temperature-controlled perfusion chamber during stimulation, achieving acquisition rates of 100-300 Hz. An accompanying open-source analysis pipeline automatically tracks presynaptic structures and extracts transient amplitude, decay kinetics, temporal ratios, and frequency-domain features.

Using BLIMPS, we quantified calcium signaling dynamics in hippocampal CA1 circuits from APOE4-associated Alzheimer's disease model mice (E4FAD+) and littermate controls (E4FAD-) at 6 and 8 months of age. Dimensionality reduction, clustering, parametric kinetic analysis, and spectral decomposition revealed distinct calcium signaling signatures between excitatory and inhibitory neuronal populations across variations in sex and age. These signatures enabled robust separation of CaMKII-positive and mDLX-positive neurons.

Relative to controls, E4FAD+ mice exhibited altered inhibitory calcium dynamics, impaired

calcium decay kinetics, and increased power in higher-frequency activity bands, consistent with disruption of excitation-inhibition balance. These differences became more pronounced with age, indicating progressive dysfunction.
These findings establish BLIMPS as a platform for multidimensional analysis of presynaptic physiology and demonstrate that calcium signaling parameters are sensitive indicators of APOE4-associated circuit dysfunction. This approach provides a framework for investigating cell-type-specific mechanisms of calcium dysregulation and network imbalance in neurodegenerative disease.

Disclosures: M.C. Potcoava: None. **Z. Zurawski:** None. **I. Lu:** None. **L.M. Tai:** None. **S.T. Alford:** None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

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Topic: B.04. Synaptic Transmission

Support: NIH grant R01MH061876
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HHMI

Title: Alternative splicing of synaptotagmin 7 tunes short-term synaptic plasticity through isoform-specific oligomerization

Authors: *N. MEHTA[1], D. LARSON[1], S. SUBRAMANI[1], S. MISHRA[1], S. KAUR[1], A. JAIN[1], E. R. CHAPMAN[2];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Univ. of Wisconsin, Madison, WI

Abstract: Synaptotagmin-7 (syt7) is a presynaptic calcium sensor that regulates short-term synaptic plasticity, but the mechanisms underlying isoform-specific function remain unclear. Here, we tested whether alternative splicing within the juxtamembrane linker controls syt7 assembly and presynaptic function. We found that the α and β isoforms undergo liquid-liquid phase separation to form condensates, whereas the γ isoform forms aggregates. These results indicate that alternative splicing of the juxtamembrane linker acts as a biochemical switch that changes the higher-order assembly state of syt7. We next used iGluSnFR imaging, a genetically encoded optical glutamate sensor, to compare presynaptic neurotransmitter release mediated by the three syt7 isoforms under matched expression conditions. These experiments revealed that syt7 isoforms are functionally divergent: they differentially regulate paired-pulse facilitation and synaptic depression during repeated stimulation. This result suggests that splice-dependent assembly of syt7 fine-tunes short-term synaptic plasticity. Finally, MINFLUX super-resolution microscopy revealed that syt7 forms nanoscale clusters at the active zone in the presynapse. This positioning places syt7 near the synaptic vesicle release machinery, supporting a model in which

splice-dependent oligomerization tunes local presynaptic function. Together, these findings identify alternative splicing of the syt7 juxtamembrane linker as a mechanism that couples protein assembly to short-term synaptic plasticity.

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Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

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Presentation Number: NANO27.06

Topic: B.04. Synaptic Transmission

Support: NIH Grant R35GM139608
NSF ACCESS BIO250149

Title: Lipid Disorder and PIP2-Regulated Clustering of Syntaxin-1 JMD-TMD Regions may contribute to Membrane Fusion Competence

Authors: *D. AN[1], M. LINDAU[2];
[2]Physiol. and Biophysics, [1]Univ. of Miami, Miami, FL

Abstract: Syntaxin-1 (Stx1) is a neuronal SNARE protein essential for synaptic vesicle docking and membrane fusion. At presynaptic active zones, Stx1 is enriched in membrane nanoclusters that are thought to regulate vesicle release, yet the molecular mechanisms governing cluster formation and membrane organization remain incompletely understood. Here, we used MARTINI coarse-grained molecular dynamics simulations to investigate how the juxtamembrane and transmembrane domains (JMD-TMDs) of Stx1A and Stx1B remodel the plasma membrane and self-assemble into oligomeric clusters.
Simulations revealed that individual Stx1 JMD-TMDs induce local membrane lipid disorder primarily through hydrophobic mismatch between the transmembrane helix and the membrane hydrophobic core. Stx1A generated stronger and more spatially extended lipid disorder than Stx1B. The magnitude of local membrane disorder remained largely independent of protein density. TMD palmitoylation spatially confined membrane perturbation, whereas depletion of phosphatidylinositol 4,5-bisphosphate (PIP2) broadened the radial extent of membrane disorder. The Stx1 JMD-TMDs showed oligomerization, promoting progressive hierarchical oligomerization from dimers and trimers to larger assemblies (cluster maturation), increasing JMD-TMD copy numbers. Cluster maturation was accompanied by merging of local lipid disordered regions and decreasing extent of localized membrane disorder zones. TMD palmitoylation and PIP2 depletion suppressed cluster maturation towards higher-order oligomers. Stx1B exhibited a greater propensity for oligomerization and was less sensitive to the inhibitory effects of TMD palmitoylation and PIP2 depletion than Stx1A.
Together, these findings support a model in which hydrophobic mismatch establishes local

membrane disorder, whereas palmitoylation and PIP2 cooperatively regulate the spatial organization and oligomerization of Stx1. The resulting modulation of membrane organization may contribute to Syntaxin's propensity to form cluster assemblies and enabling fusion competent SNARE states promoting neurotransmitter release.

Disclosures: D. An: None. **M. Lindau:** None.

Nanosymposium

NANO27: Presynaptic Structure, Organization, and Function

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Presentation Number: NANO27.07

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Brain & Behavior Research Foundation (32147)

Title: Soluble α2δ-1 acts as an activity-regulated modulator of cortical circuit homeostasis and restores sociability and cognition in a mouse model of schizophrenia

Authors: *M. DOS SANTOS[1], M. P. FORREST[1], E. BOMBA-WARCZAK[2,3], S. DEY[1], E. L. PARNELL[1], J. M. CHRISTIANSEN[1], K. YANG[4], L. N. HAYES[5], J. M. COUGHLIN[4], B. ECKMAN[1], C. LAMMERT[6], M. D. MARTIN-DE-SAAVEDRA[7], M. MARTINA[8], A. SAWA[4], J. N. SAVAS[2], P. PENZES[1];
[1]Neurosci., [2]Neurol., Northwestern Univ., Chicago, IL; [3]Physiol., Univ. of Pennsylvania, Philadelphia, PA; [4]Psychiatry, Johns Hopkins Univ., Baltimore, MD; [5]Cell Biol., Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [6]Biotech, Chicago, IL; [7]Complutense Univ., Madrid, Spain; [8]Neurosci., Northwestern Univ. Med. Sch., Chicago, IL

Abstract: Neuronal connection dysfunction and disrupted excitation-inhibition (E/I) balance are convergent mechanisms underlying cognitive deficits in schizophrenia (SCZ) and other brain psychiatric disorders. Although membrane-bound synaptic proteins are essential regulators of neuronal communication, their shed soluble ectodomains remain largely unexplored as extracellular modulators of circuit function.
Using quantitative proteomics of human cerebrospinal fluid (CSF), we identified a soluble form of the voltage-gated calcium channel auxiliary subunit α2δ-1, encoded by the gene CACNA2D1, that is robustly reduced in individuals with SCZ. Combining super-resolution STED microscopy, 2photon calcium imaging, and biochemical methods, we show that soluble α2δ-1 is released by

the brain in an activity-dependent manner and binds synaptic targets to reorganize neuronal network dynamics *in vitro* and *in vivo*. Its synthetic analog, which we called "SEAD1" (the **S**ynthetic **E**ctodomain of **A**lpha2**D**elta-**1**), enhances parvalbumin-positive interneuron function, promotes inhibitory neuron plasticity, and modulates E/I balance.
Remarkably, a single prefrontal cortical injection of SEAD1 rescued interneuron, synaptic, cognitive, and social deficits in a genetic mouse model of the 16p11.2 duplication syndrome, which is associated with SCZ and autism.
We are now using *in vivo* two-photon calcium imaging combined with AI-markerless pose estimation to assess the real-time effects of SEAD1 on cortical circuit activity in behaving animals.
These findings highlight soluble synaptic ectodomains as a previously overlooked class of activity-dependent intercellular signaling molecules, which could have therapeutic potential to improve brain function in neuropsychiatric and cognitive disorders.

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Nanosymposium

NANO28: Alzheimer's Disease and Aging: Imaging

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO28.01

Topic: J.07. Data Analysis and Statistics

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Kavli Neuroscience Discovery Institute

Title: Digital Pathology Across Scales in Alzheimer's Medial Temporal Lobe

Authors: *D. MATHEW[1], D. PREMATHILAKA[2], Y. XIE[3], J. T. RATNANATHER[2], M. I. MILLER[2];
[2]Dept. of Biomed. Engin., [3]Dept. of Electrical and Computer Engin., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Alzheimer's disease leaves its mark at every scale of brain organization, from dysregulated gene expression to the progressive loss of macroscopic structure. Emerging

technologies now capture these signals at molecular, cellular, and macroscopic scales. Yet without a way to link them in the same tissue, each scale remains an incomplete picture of the same disease. We present a framework that can co-register high-field MRI, histology, and spatial transcriptomics to the human medial temporal lobe, the earliest site of Alzheimer's disease pathology. In this study, human postmortem MTL tissue was sectioned and prepared across four modalities: high-field MRI acquired prior to sectioning, Nissl-stained, tau immunostained sections, and spatial transcriptomics sections. These four modalities span the full spatial hierarchy of the disease from MRI at millimeter resolution down to gene expression counts at the micron resolution. Using xIV-LDDMM, a particle-based large deformation diffeomorphic metric mapping approach, spatial transcriptomics and Nissl sections were registered into the coordinate system of the tau-stained tissue. Those same slices, now in tau coordinates, were then registered to the 3D MRI volume space. For each slice, the corresponding location in the Mai Paxinos Atlas was also determined. With this framework, we built a rendering agent to process, display, and compute statistics on the petascale dataset. Using Jacobian determinants of the deformation field to confirm integrity, we achieved accurate full co-registration of high-resolution Nissl, tau, and spatial transcriptomics for five slices through a high-field MRI. Additionally, our rendering agent efficiently manages the computational demands of multi-scale data spanning six orders of magnitude in resolution, handling over 60 GB of cross-modal registrations in real time with a frame rate of 59FPS (± 3). Together, these modalities form a single, interactive view of the diseased brain that can be queried from the scale of a gene to the scale of a brain region.



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Nanosymposium

NANO28: Alzheimer's Disease and Aging: Imaging

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO28.02

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

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the Kavli Neuroscience Discovery Institute

Title: Amygdala and Entorhinal Cortex Neurodegeneration Tracks Tau Pathology and Provide Complementary Biomarkers Beyond Hippocampus in Alzheimer's Disease

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Abstract: Neurodegeneration in Alzheimer's disease (AD) is often evaluated using hippocampal atrophy, yet neuropathological studies suggest that other medial temporal lobe (MTL) regions, such as the amygdala and entorhinal/trans-entorhinal cortex (ERC/TEC), are affected earlier in the disease process. We investigated regional relationships among amyloid burden, tau accumulation, neurodegeneration, and diagnostic status using longitudinal multimodal imaging from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The study included 1019 subjects (387 controls, 523 MCI, and 109 AD) with ≥3 longitudinal T1 MRI scans to estimate volume atrophy. A multimodal subset with AV1451 tau PET and AV45 amyloid PET data (118 subjects, 994 imaging sessions) was used to evaluate associations among amyloid burden, tau accumulation, and neurodegeneration. We used an automated nnU-Net to segment the amygdala, ERC/TEC, and hippocampus, achieving high agreement with manual delineations (Dice 0.81-0.96). Regional volumes were measured from longitudinal MRI, and annualized volume atrophy rates (% / year) were estimated using subject-specific linear regression. Mean atrophy rates increased monotonically from controls to MCI and AD, with ERC/TEC and amygdala degeneration consistently exceeding hippocampal degeneration. In AD, amygdala and ERC/TEC atrophy exceeded hippocampal atrophy by more than twofold (7.19 % / yr and 8.40 % / yr vs. 3.23 % /yr). Standardized uptake value ratio (SUVR) for Tau PET was strongly associated with atrophy rate in amygdala ($r = 0.807$), ERC/TEC ($r = 0.717$), and hippocampus ($r = 0.619$) (all $p < 0.001$) in the high-amyloid group. In contrast, amyloid SUVR showed substantially weaker and inconsistent associations with atrophy, indicating that amyloid deposition alone is not a strong predictor of ongoing structural degeneration. To evaluate clinical utility, we performed Cognitively Normal (CN) versus early MCI (EMCI) classification using regional volume and atrophy features from 556 subjects (346 CN, 210 EMCI). A logistic regression model using amygdala and ERC/TEC measures achieved a significantly higher AUC than a hippocampus-only model (Wilcoxon $p<0.01$), with specificity increases of 9.7% and 8.2% at sensitivities of 0.80 and 0.85, respectively. These findings suggest that AD-related neurodegeneration is distributed across MTL structures rather than predominantly hippocampal and is directly linked

to regional tau in subjects with high amyloid burden. Incorporating amygdala and ERC/TEC measurements can improve MRI-based detection of early AD-related neurodegeneration and provide complementary biomarkers for disease staging.

Disclosures: Y. Xie: None. **M.O. Morris:** None. **C. ceritoglu:** None. **L. Younes:** None. **J.T. Ratnanather:** None. **M. Miller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MIM is a founder of and holds equity in AnatomyWorks. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies..

Nanosymposium

NANO28: Alzheimer's Disease and Aging: Imaging

Location: WCC Rm 140

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Presentation Number: NANO28.03

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

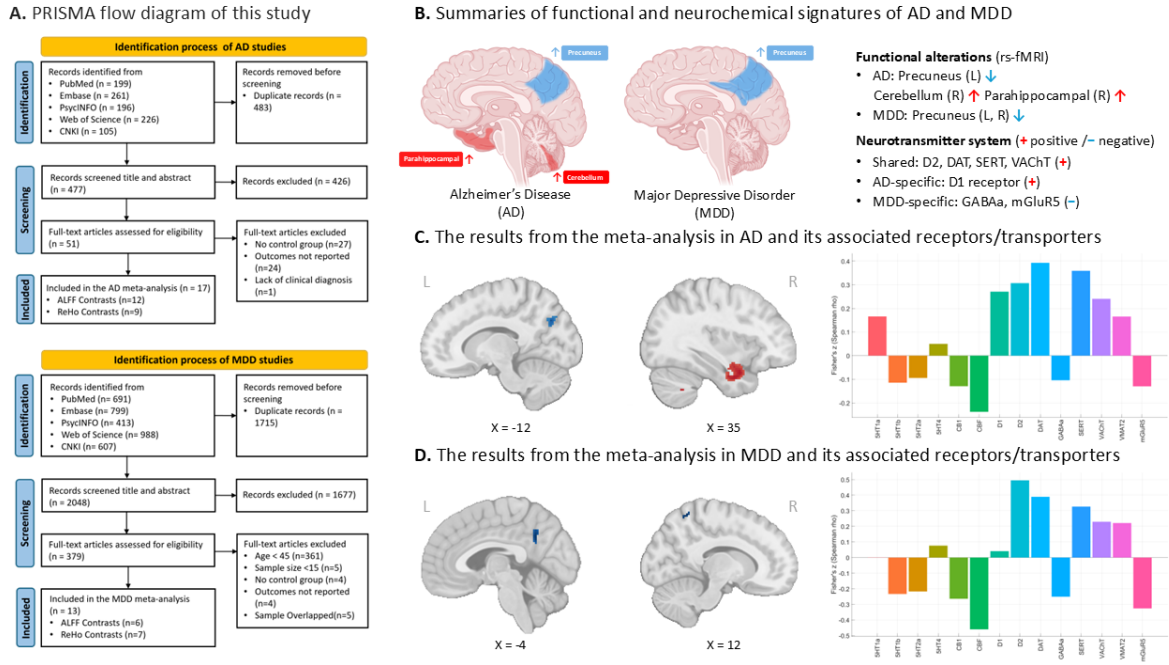
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Title: Resting-state activity alterations in Alzheimer’s disease and major depressive disorder: a coordinate-based meta-analysis

Authors: *Y. MAO[1], H. DING[1], M. YUE[1], W. CHAN[1], P. LEE[1], C. LAW[1], E. CHAN[1], Y. WONG[1], H. CHEN[1], J. LAN[1], G. YIP[1], N. NG[1], K. OH[2,1], G. CHENG[1], J. YOO[1];
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Abstract: Both Alzheimer’s disease (AD) and major depressive disorder (MDD) have been reported hippocampal and posterior cingulate cortical atrophy and reduced default mode network connectivity, suggesting potential shared neuropathology. Resting-state fMRI provides a useful approach for assessing spontaneous activity. The metrics for quantifying regional activity include regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and fractional ALFF. However, these findings remain inconsistent within and between AD and MDD. Hence, we conducted two coordinate-based meta-analyses in AD and MDD in a pre-registered protocol. The outcomes of these two meta-analyses are ReHo and ALFF. Studies were eligible if they (1) compared patients with healthy controls (HCs); (2) diagnosed patients using standardized criteria; (3) included ≥ 12 patients; and (4) reported a mean age of ≥ 45 years. We excluded studies with comorbid AD and MDD patients. The final sample included 17 AD experiments (457 patients, 362 HCs) and 15 MDD experiments (318 patients, 262 HCs). Meta-analyses were performed in Seed-based d Mapping with family-wise error correction ($p < 0.05$). The AD meta-

analysis showed increased activity in the right parahippocampal gyrus and cerebellum, along with decreased activity in the left precuneus. The MDD meta-analysis showed decreased activity in the bilateral precuneus, with no regions showing significant increases. To further interpret these findings, we spatially correlated AD and MDD patterns with PET-derived neurotransmitter system maps (JuSpace v2.1). Both AD and MDD showed positive spatial correlations with D2, DAT, SERT, and VAChT maps. AD showed a positive correlation with the D1 map, whereas MDD showed negative correlations with GABAa and mGluR5 maps. The findings highlight the precuneus as a shared site of alteration in AD and MDD, and parahippocampal hyperactivity and D1-related spatial associations may serve as AD-specific markers.



Disclosures: Y. Mao: None. **H. Ding:** None. **M. Yue:** None. **W. Chan:** None. **P. Lee:** None. **C. Law:** None. **E. Chan:** None. **Y. Wong:** None. **H. Chen:** None. **J. Lan:** None. **G. Yip:** None. **N. ng:** None. **K. Oh:** None. **G. Cheng:** None. **J. Yoo:** None.

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

Title: Early Alzheimer's Risk Index (EARI): A Novel 21-Domains Scoring Framework)

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Abstract: Abstract Alzheimer's disease (AD) is known as complex neurodegenerative disorder that is recognized as a progressive condition that develops long before clinical symptoms become visible and are recognized. According to the report, Alzheimer's disease is thought to begin 20 years or more before symptoms arise, with early brain and metabolic changes occurring silently during the preclinical phase of the disease. Although current guidelines cover several domains, they remain fragmented and often overlook the interplay between peripheral and central mechanisms. To address this gap, this 21-item Early Alzheimer Risk Index (EARI) provides a potential framework that integrates multiple AD pathophysiology, developed through structured domain mapping and synthesis of multidisciplinary evidence and categorized into core and optional domains. The core domains (10 items) include Genetics (APOEε4, TREM2), cognitive screening, longitudinal decline, gold-standard biomarkers (amyloid, tau) imaging MRI white matter hyperintensities (WMH), hyponatremia in long follow-up period carried higher risk of dementia including both AD and non-AD. (Chung et al.,2017), cardiovascular comorbidity, and metabolic dysfunction factors such as insulin resistance, and acidosis condition in lysosomal acidification impairment in early AD that impact microglia and increase the abnormal hyperphosphorylation of tau protein in vitro (Basurto-Islas et al.,2013). Optional domains (11 items) enhance sensitivity including neuroinflammation such as IL-10 dysregulation, cytokines IL- 1β,IL-6,TNF-α, astrocytic dysfunction that drive white matter damage, environmental exposure (pesticides, herbicides and other endocrine disrupting chemicals such as Bisphenol A (BPA)) that induce amyloid-β accumulation, cholesterol imbalance for amyloid deposition, blood gas abnormalities impacted microglial function, renal dysfunction, cardiomegaly indices, olfactory deficits, infectious burden, gut microbiome, EEG or functional imaging, and lifestyle factors (diet, activity, sleep). Together these domains form Early Alzheimer's Risk Index (EARI) that complement existing guidelines, by bridging peripheral and central mechanisms provides a comprehensive practical tool to evolve AD therapy in clinical decision-making.

Disclosures: H. pristiwa oktaviani: None. **R.B. mboe:** None.

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

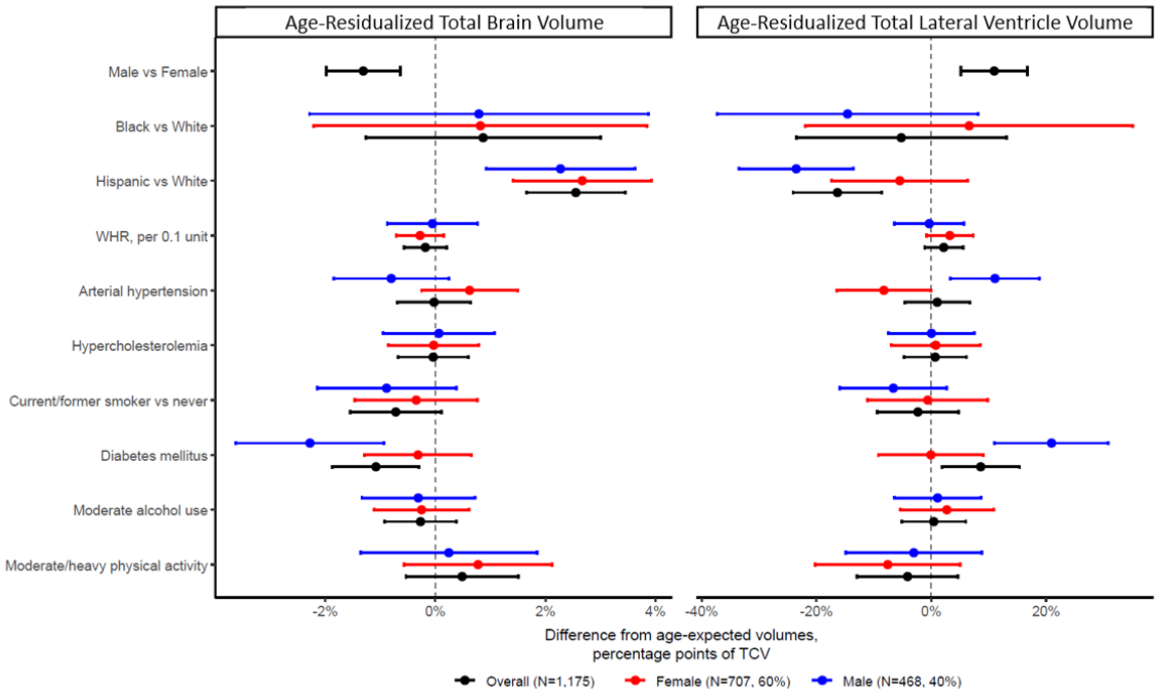
Support: T32 AG081170
R01 NS029993
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Title: Sex Differences in Associations of Traditional Vascular Risk Factors with Cerebral Volume Loss Beyond Aging in the Northern Manhattan Study

Authors: *M. NAFELI SHAHRESTANI[1,2,3], C. AGUDELO[2,3], H. GARDENER[2,3], M. DI TULLIO[4], M. S. V. ELKIND[5], C. B. WRIGHT[6], J. GUTIERREZ[2], S. TOM[7], T. RUNDEK[2,3]; [1]Univ. of Miami, Coral Gables, FL; [2]Dept. of Neurol., [3]Evelyn F. McKnight Brain Inst., Univ. of Miami Miller Sch. of Med., Miami, FL; [4]Dept. of Med., [5]Dept. of Neurol., Columbia University, Vagelos Col. of Physicians and Surgeons, New York, NY; [6]Natl. Inst. of Neurolog. Disorders and Stroke (NINDS), NIH, Bethesda, MD; [7]Dept. of Epidemiology, Mailman Sch. of Publ. Health, Columbia Univ., New York, NY

Abstract: Aging is accompanied by brain tissue volume reduction and compensatory expansion of brain ventricles. Traditional vascular risk factors (RFs) may contribute to age-disproportionate cerebral atrophy. We hypothesized that diabetes mellitus (DM), hypertension (HTN), and other RFs are associated with MRI markers of cerebral atrophy in dementia- and stroke-free Northern Manhattan Study participants, with sex differences in these associations. Total brain volume (TBV) and total lateral ventricle volume (TLV), quantified on MRI using DeCarli volumetric method, were normalized to total cranial volume (TCV). TBV/TCV and TLV/TCV were age-residualized to capture deviations from age-expected volumes and modeled using multivariable linear regression, including demographics and RFs, in all and in sex-stratified subgroups ($\alpha = 0.05$). Sex interactions were tested for each RF in separate models ($\alpha = 0.10$). Among 1,175 participants (mean age 70 ± 9 years, 60% women), mean TBV/TCV and TLV/TCV were 72.5 ± 4.3% and 3.2 ± 1.5%. Men had lower TBV/TCV ($\beta = -0.95$) and greater TLV/TCV ($\beta = 0.35$; Figure) than women. Sex modified the associations of HTN and DM with both volume markers (interaction p values < 0.10). In men, relative to cohort means, DM was associated with 2.3% lower TBV/TCV ($\beta = -1.64$; 95% CI: −2.6, −0.67) and with 21% greater TLV/TCV ($\beta = 0.72$; 95% CI: 0.38, 1.10). DM associations were also statistically significant overall, but not in women ($p > 0.05$). HTN was associated with greater TLV/TCV in men ($\beta = 0.38$; 95% CI: 0.12, 0.65), but smaller TLV/TCV in women ($\beta = -0.25$; 95% CI: −0.51, 0.00). In this community-based cohort of middle-aged to older adults, traditional vascular RFs showed sex-specific associations with cerebral and ventricular volumes beyond expected aging, with stronger and more consistent associations in men. Diabetes appeared as a male-specific correlate of both volume markers, suggesting greater vulnerability to structural neurodegenerative changes. Defining sex-specific vascular risk profiles may help identify targeted strategies to preserve brain health with aging.

Figure. Vascular Risk Factors of Age-Residualized Cerebral and Lateral Brain Ventricle Volumes



Forest plots show adjusted β estimates and 95% confidence intervals for age-residualized TBV/TCV on the left and TLV/TCV on the right. Black represents the overall cohort; red and blue represent women and men, respectively. The x-axis represents percentage-point differences from age-expected volume relative to total cranial volume. Negative values for TBV/TCV indicate smaller cerebral volume than expected for age, whereas positive values for TLV/TCV indicate greater ventricular volume than expected for age. Abbreviations: BMI = Body Mass Index; WHR = Waist-to-Hip Ratio; TBV = Total Brain Volume; TLV = Total Brain Lateral Ventricles Volume; TCV = Total Cranial Volume.

Disclosures: M. Nafeli Shahrestani: None. **C. Agudelo:** None. **H. Gardener:** None. **M. Di Tullio:** None. **M.S.V. Elkind:** None. **C.B. Wright:** None. **J. Gutierrez:** None. **S. Tom:** None. **T. Rundek:** None.

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

Support: NIH Grant P20GM109025
Cleveland Clinic Neurological Institute Emergent Clinician-Scientist Career Development Award

Title: White matter network organization predicts longitudinal cognitive decline in a clinical aging cohort

Authors: *A. R. BENDER[1], Z. YANG[2], P. R. PATTIAM GIRIPRAKASH[1], K. A. MARTINEZ[1], J. DAMOISEAUX[3];
[1]Lou Ruvo Ctr. for Brain Hlth., [2]Cleveland Clin., Las Vegas, NV; [3]Wayne State Univ., Detroit, MI

Abstract: Introduction. Older age and Alzheimer's disease (AD) are associated with white matter disconnection and altered structural connectome topology (SCT), which may precede cognitive decline. Despite prior whole brain SCT work in AD, subnetwork properties remain understudied. We hypothesized that graph theoretic measures of SCT trajectories predict cognitive decline, and that baseline amyloid moderates SCT change in a clinical aging cohort.
Methods. Participants (N=176; mean age = 71.4, SD = 7.3 years; 49% female) included cognitively unimpaired adults (CU; n=91) and those diagnosed with mild cognitive impairment (MCI; n=57) or AD dementia (n=28); all had baseline amyloid PET (centiloid) and longitudinal dMRI and cognitive testing (mean 1.9 visits, ~1.5-yr intervals). dMRI data were processed using MRtrix3 ACT and Schaefer200/Yeo7 parcellation to estimate 71 fiber density-weighted graph metrics (path length, efficiency, modularity, hub strength) across 8 network tiers (whole brain [WB], default mode [DMN], limbic [LIM], salience/ventral attention [SVAN], control [CONT], dorsal attention [DAN], somatomotor [SOM], visual [VIS]). Linear mixed-effects models tested Time × metric interactions as predictors of 4 cognitive outcomes (RAVLT delayed recall, TMT-A/B, animal fluency), covarying for age, sex, clinical status, centiloid, and conversion history; we applied FDR correction within each outcome. Separately, we tested Time × Centiloid interactions in 4 whole brain SCT metrics.
Results. Multiple SCT metrics predicted semantic fluency decline (animals naming), independent of amyloid: path length (WB), hub/efficiency (WB), coreness/small-worldness (LIM), modularity/coreness (SVAN), hub strength (VIS), coreness (CONT; all $p_{FDR} < 0.05$). Higher CONT small worldness predicted faster TMT-A speed (β/SD = +0.13, $p_{FDR} = 0.036$), suggesting frontoparietal network topology supports speeded processing. Baseline amyloid moderated whole brain SCT trajectories: age-expected modularity increases in low-amyloid subjects (+0.007/yr, $p = 0.017$) were absent in high-amyloid ($\beta \approx 0$, $p = 0.95$); global efficiency and path length also diverged ($p_{FDR} < 0.05$). Convergent effects across DMN, LIM, and SVAN suggest domain-specific SCT-cognition coupling.
Conclusion. Ongoing SCT changes in AD-vulnerable networks predict declines in semantic fluency and speeded processing independently of amyloid; however, amyloid burden nullifies aging-related modularity increases, consistent with a preclinical structural disconnection cascade in AD.

Disclosures: A.R. Bender: None. **Z. Yang:** None. **P.R. Pattiam Giriprakash:** None. **K.A. Martinez:** None. **J. Damoiseaux:** None.

Nanosymposium

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

Support: NIH Grant R01AG081655
NIH Grant K23AG070320

Title: Distinct neural correlates of rule breaking and aggressive behaviors in frontotemporal dementia

Authors: *B. AKBARIAN, R. DARBY;
Neurol., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Antisocial behaviors are common in frontotemporal dementia (FTD), but the neural mechanisms underlying these behaviors remain unclear. Prior evidence also suggests the mechanisms leading to rule-breaking vs. aggressive antisocial behaviors may be distinct. Here, we examined whether rule-breaking and aggressive behaviors were increased in FTD syndromes vs. controls and relate to neuroimaging abnormalities in frontotemporal regions. Caregivers of 23 with behavioral variant FTD (bvFTD), 10 with semantic variant primary progressive aphasia (svPPA), 13 with nonfluent variant primary progressive aphasia (nfvPPA), and 16 controls (HC) completed the Adult Behavior Checklist (ABCL), a measure of rule-breaking and aggressive behaviors. We examined differences in ABCL scores between groups, and associations with grey matter volume, and cerebral blood flow (CBF), controlling for age, sex, and diagnosis. Compared with controls, rule-breaking scores were higher in bvFTD and svPPA, whereas antisocial scores were higher in bvFTD; aggressive behavior did not differ significantly. Higher rule-breaking scores were associated with lower gray matter volume and lower CBF in orbitofrontal / ventromedial prefrontal cortex (OFC/vmPFC) and anterior temporal lobe (ATL). Whole-brain voxel-wise analyses showed that the negative associations with grey matter volume extended into the anterior insula, anterior cingulate, and ventral striatum / nucleus accumbens, whereas negative associations with CBF extended into superior frontal and dorsolateral prefrontal cortices. CBF added explanatory value beyond gray matter volume in left ATL, and visual comparison of whole-brain results suggested that CBF and gray matter volume showed partly distinct spatial patterns related to rule-breaking behavior (Fig. 1). Our results support that rule-breaking but not aggressive antisocial behaviors are increased in FTD and neural changes in the OFC/vmPFC, ATL, and related regions, with structural and functional neuroimaging providing distinct but complementary information.

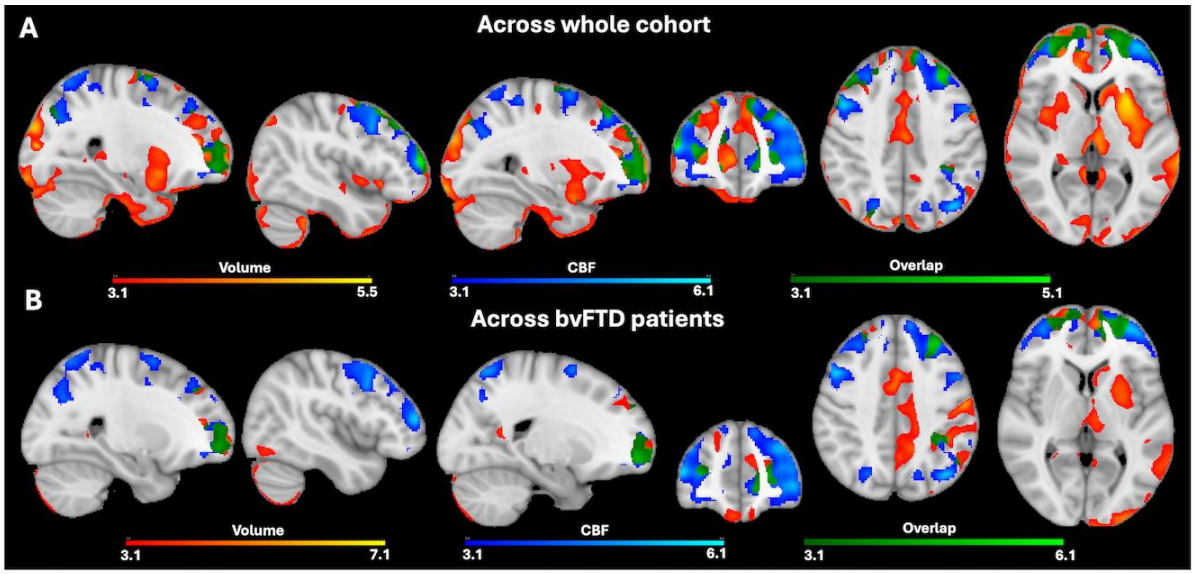


Fig 1. Structural and perfusion correlates of rule-breaking behavior. Brain regions associated with rule-breaking behavior across the full cohort (A) and within the bvFTD subgroup (B). Blue regions represent areas in which higher rule-breaking scores were significantly associated with reduced cerebral blood flow (CBF), and red regions represent areas in which higher rule-breaking scores were significantly associated with reduced gray matter volume and yellow regions were associated with overlap between volume and CBF. The partially distinct spatial distributions indicate that structural and perfusion measures capture overlapping but non-identical aspects of the neural substrates underlying rule-breaking behavior.

Disclosures: B. Akbarian: None. **R. Darby:** None.

Nanosymposium

NANO29: Neural Circuits of Reward and Appetitive Learning and Memory

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO29.01

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant DK134804

Title: Semaglutide-induced decrease in food seeking is regulated by prelimbic cortex to nucleus accumbens circuit

Authors: *Y. LI[1], K. ARBUCKLE[2], L.-C. CHAO[3], A. K. SUTTON HICKEY[4], A. LEGARIA[5], B. A. MATIKAINEN-ANKNEY[6];
[1]Rutgers Univ., Piscataway, NJ; [2]Rutgers, Piscataway, NJ; [3]Rutgers University–New Brunswick, Piscataway, NJ; [4]Dept. of Psychology and Neurosci., Temple Univ., Philadelphia, PA; [5]Neurosci., Washington Univ. in St. Louis, Saint Louis, MO; [6]Psychology, Rutgers Univ. Behavioral and Systems Neurosci., Piscataway, NJ

Abstract: Semaglutide (SEMA), a GLP-1R agonist prescribed for obesity and diabetes, reliably reduces food intake. While GLP-1R agonism regulates food intake, appetite, and glycemic control, it is increasingly recognized as regulating consumption behaviors across disorders, including alcohol and substance use disorder. This suggests SEMA may reduce consumption by

broadly dampening motivation. However, how SEMA alters motivational and decision-making processes remains poorly understood. We addressed this in C57BL/6J mice using home cage operant assays: fixed-ratio (FR) responding, a closed-economy resetting progressive ratio (PR) task, probabilistic reversal learning, and passive infrared locomotor monitoring. Acute SEMA (0.025 mg/kg, IP) rapidly reduced FR responding for sucrose and decreased breakpoint, meal size, and total pellet consumption on the PR task without altering locomotor activity, arguing against generalized malaise. SEMA did not impair performance on a reversal learning task. Using a closed-economy task with a resetting progressive ratio schedule, we observed that SEMA decreased both food intake and willingness to exert effort for food. These effects occurred without changes in physical activity, indicating that reduced performance was likely not due to general malaise, although we did not rule out a role for gastrointestinal malaise in driving reductions in food intake. Computational reinforcement learning modeling revealed SEMA significantly shifted positive learning rates, negative learning rates, and choice-history weighting, yet reversal accuracy was preserved. SEMA-treated mice showed decreased Win-Stay and increased Lose-Shift behavior, indicating contingency learning was maintained while sensitivity to recent reward history was attenuated. To probe circuit mechanisms, we chemogenetically inhibited prelimbic cortex to nucleus accumbens (PL-NAc) projection neurons using cre-dependent hM4Di DREADDs. PL-NAc inhibition alone increased breakpoint without affecting reversal learning, establishing this projection as a selective brake on effortful food pursuit. Critically, PL-NAc inhibition rescued SEMA-induced reductions in food seeking by restoring meal size. The computational signature of SEMA was not replicated by PL-NAc inhibition alone, suggesting learning-rate effects arise via parallel mechanisms. These findings demonstrate that acute GLP-1R activation selectively constrains motivational drive without impairing adaptive decision-making, and identify PL-NAc circuitry as a necessary substrate for SEMA-induced reductions in effortful food seeking.

Disclosures: Y. Li: None. **K. Arbuckle:** None. **L. Chao:** None. **A.K. Sutton Hickey:** None. **A. Legaria:** None. **B.A. Matikainen-Ankney:** None.

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Presentation Number: NANO29.02

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant
Simons foundation

Title: Brainwide circuit-specific fMRI reveals afferent projection activity during reward stimulation

Authors: *W. TU, J. WEN, J. MEDRANO, A. JASANOFF;
Biol. Engin., MIT, Cambridge, MA

Abstract: Motivated behavior, learning, and decision-making depend on the concerted function of a set of neural structures that together make up the brain's reward system. Studying how neural information propagates among these structures during stimuli and tasks could reveal fundamental network-level bases of reward-related brain functions such as the computation of reward prediction error signals and the changing representations of rewarded stimuli or actions. We recently introduced a neuroimaging approach that enables us to perform such studies using a genetically encoded neural activity probe that is detectable at a brain-wide scale by functional magnetic resonance imaging (fMRI). Delivery of the probe, called NOSTIC, using a retrogradely transported virus, permits selective fMRI of presynaptic inputs to sites of viral injection. We applied this strategy to structures in the reward network in rats, obtaining spatially comprehensive activity measurements of input to key reward processing areas from around the brain. We describe how this approach identifies components of reward circuitry that track reward magnitude and history in a passive rewarding stimulation paradigm. We also show how NOSTIC-based fMRI can be used to study how the same circuit elements represent reward and learning-related variables in a classical conditioning task implemented in awake animals. Our results suggest circuit-level contributions to reward prediction-related calculations, probe the representation of behavioral variables by specific circuit elements, and help define roles of neurochemically distinct systems in integrated operation of the reward system.

Disclosures: W. Tu: None. **J. Wen:** None. **J. Medrano:** None. **A. Jasanoff:** None.

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Presentation Number: NANO29.03

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Central amygdala D1-neuron and astrocyte signaling during feeding

Authors: *E. UPPALAPATI, D. KERSPERN, A. LUTAS;
Natl. Inst. of Diabetes and Digestive and Kidney Dis., NIH, Bethesda, MD

Abstract: Feeding is a complex behavior that requires the integration of external sensory cues with internal physiological states to guide goal-directed actions. The central amygdala (CeA) serves as a critical hub for reward processing, affective valence, and the regulation of feeding. Previous studies indicate that astrocytes actively regulate signaling transmission of the local neuronal network in the CeA. While astrocytes are increasingly recognized as modulators of neuronal network activity, their role in feeding-related behaviors remains poorly understood. Previously, we found that dopamine is released in the CeA during feeding. To further explore the role of dopaminergic cells in consummatory behaviors, we monitored calcium biosensor dynamics in dopamine receptor 1 (D1)-expressing neurons in the CeA of mice engaged in Pavlovian feeding tasks using fiber photometry. This revealed that D1 neuronal activity is modulated during ingestion, independent of internal state, and does not respond to reward-

predictive cues. Next, we performed RNAscope in situ hybridization, which revealed that GFAP, a biomarker for astrocytes, colocalized with Drd1 mRNA, indicating crosstalk between astrocytes and dopaminergic receptors. We then replicated our fiber photometry experiments to monitor calcium activity of astrocytes in the CeA during Pavlovian feeding tasks, and found astrocyte activity is also modulated during ingestion, independent of internal state, but also seems to respond to motor actions related to feeding, such as licking. Moreover, astrocytic calcium dynamics track consummatory actions and appear insensitive to the identity or sensory properties of the ingested tastant. To further test if astrocytes are directly involved in the dopaminergic signaling we observed during feeding, we performed calcium biosensor imaging via 2-photon microscopy on ex vivo brain slices from mice, and confirmed that astrocytes directly respond to dopamine independently of neuronal activity. Collectively, these results suggest that CeA astrocytes can directly detect dopamine and show elevated calcium in response to feeding. Furthermore, they support a role for astrocytes in CeA processing during consummatory behavior, positioning them as potential contributors to the neural mechanisms underlying feeding regulation.

Disclosures: E. Uppalapati: None. **D. Kerspern:** None. **A. Lutas:** None.

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McCamish Blue Sky Grant
Petit Lanier Fellowship to TK
NIH NIBIB T32EB025816

Title: Stimulus- and Reward-driven Dopamine Dynamics During Behavioral Change

Authors: C. WAIBLINGER[1], N. H. P. CHANG[2], E. ULUTAS[1], S. RUSSO[1], D. A. WEISS[1], F. FIROZ[1], T. KAMAL[3], J. E. MARKOWITZ[1], ***G. B. STANLEY**[1];
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Abstract: Dopamine (DA) is required to form associations between sensory cues and rewarding outcomes which is fundamental for reward-guided learning. How DA signaling is modulated across distinct behavioral stages, including acquisition, task proficiency, and adaptation to changing sensory environments, remains unknown. This study focuses on dissecting the role of DA in adaptive behavior in changing sensory environments. We longitudinally measured DA signaling in the nucleus accumbens (NAc) using dLight1.1 photometry in head-fixed mice performing a whisker-based detection task across distinct behavioral stages, including classical

conditioning, extended operant conditioning with delayed reward, and adaptation to high- and low-range stimulus distributions.During classical conditioning, stimulus-related and reward-related transients rapidly emerged. Delayed reward delivery revealed temporally distinct DA-Stim and DA-Reward signals that persisted throughout extended training. These results are consistent with previous NAc photometry studies showing the emergence of stimulus-related DA signals during learning and persistent stimulus- and reward-related DA components after training.Stimulus-evoked DA responses were larger on Hit than Miss trials, with the strongest outcome-dependent modulation observed during early operant learning. As animals approached stable task proficiency, both DA-Stim and DA-Reward transients progressively attenuated despite continued improvements in performance. During adaptation to changing stimulus statistics, identical stimulus amplitudes evoked larger DA transients and improved detection performance in the low-range compared with the high-range context.These findings reveal distinct phases of DA signaling across learning. DA transients emerge during acquisition, attenuate with proficiency, and are selectively enhanced during adaptation to changing sensory environments, suggesting that DA signaling is most strongly engaged during periods of behavioral change, including the acquisition and updating of behavioral strategies.

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Nanosymposium

NANO29: Neural Circuits of Reward and Appetitive Learning and Memory

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO29.05

Topic: H.02. Reward and Appetitive Learning and Memory

Support: F32 DK135401

Title: The pedunculopontine nucleus acts as an essential gateway for dopamine-driven associative learning

Authors: *N. K. SMITH[1], R. WU[1], M. AWH[3], A. YEUNG[2], J. BETLEY[2];
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Abstract: As we move through the world, our brain is constantly generating predictions. A central signal for predictive coding in the brain emanates from dopamine neurons in the ventral tegmental area. When an animal encounters an unexpected reward, dopamine neurons are activated and over learning this activation shifts to the environmental cues that reliably preceded reward. This shift is thought to depend on synaptic plasticity at excitatory inputs to dopamine neurons, however the source of this excitatory input has not been determined. Here we investigate the connection between the pedunculopontine nucleus, an evolutionarily conserved region of the midbrain, and the ventral tegmental area to determine whether it is involved in this

fundamental plasticity of learning. We find that the pedunculopontine nucleus is required for dopamine release to salient stimuli across the brain, and that its inhibition renders animals unable to acquire Pavlovian conditioning for both food or an aversive shock. Using endoscopic calcium imaging, spatial transcriptomics, patch clamp electrophysiology, and anatomically/genetically constrained viral tools, we show that the projection from the pedunculopontine nucleus to the dopamine system is made up of a functionally and genetically diverse set of neurons. These neuronal clusters form separable circuits that support distinct aspects of dopamine release and associative learning. These findings define the neural architecture that enables dopamine release to fundamental stimuli like food and pain. Further, they position the pedunculopontine nucleus as an essential contributor to dopaminergic predictive coding and provide a platform to investigate how neural components for basic associative learning are corrupted in maladaptive states like disordered eating, chronic stress, and psychiatric conditions.

Disclosures: N.K. Smith: None. **R. Wu:** None. **M. Awh:** None. **A. Yeung:** None. **J. Betley:** None.

Nanosymposium

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: Bipotential plasticity of VTA GABA neurons is partially output specific

Authors: *S. HOFFMAN[1], J. EDWARDS[2], R. BONNEY[1], M. DAHL[1], T. FULLER[1];
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Abstract: Synaptic plasticity within the ventral tegmental area (VTA) is a process facilitating reward learning and memory. Understanding synaptic plasticity within the inhibitory networks of the VTA is essential to build a complete knowledge of the reward system under normal physiological conditions. Previously, our lab identified that a 5Hz stimulus induced either inhibitory long-term potentiation (iLTP) or inhibitory long-term depression (iLTD) of GABAergic inputs to VTA GABA cells in mice. VTA GABA cell electrophysiology recordings revealed that iLTP is present in ~50% of recorded cells and iLTD in the other ~50%. While iLTD is $GABA_B$ receptor-dependent, and iLTP is partially N-methyl-D-aspartic acid receptor (NMDAR) dependent, it is unknown if other mechanisms are driving the induction of iLTP or iLTD. In prior studies, we illustrated that plasticity of these VTA GABA cells is input selective, GABA neurons receiving inhibitory input from the lateral hypothalamus and rostromedial tegmental nucleus exhibit iLTP and local VTA inputs to VTA GABA cells exhibit iLTD. Since VTA GABA neurons innervate local dopamine (DA) cells and/or regions outside the VTA such as the nucleus accumbens (NAc), we hypothesize that plasticity type could be explained by VTA

GABA cell outputs. To examine VTA interneurons we employed synaptic tracer in the form of Cre- dependent helper virus followed by a deficient rabies mCherry virus. Next, we recorded GFP+/mCherry GABA interneurons using electrophysiology, which exhibited iLTP in response to 5Hz stimulus (iLTP, VTA GABA to VTA DA: $p<0.0001$ compared to baseline, ANOVA, n=13). Next, we examined projection GABA neurons by injecting red retrobeads into distinct areas of the reward circuit of GAD67GFP+ mice to label and record VTA GABA neurons projecting to the NAc, lateral habenula (LHb), and ventral pallidum (VP). These cells also exhibited iLTP in response to 5Hz stimulus with the exception of the VP which exhibited both iLTP and iLTD (VTA GABA to NAc iLTP: $p<0.0001$ compared to baseline, ANOVA, n=12. VTA GABA to LHb iLTP: $p<0.0001$, ANOVA, n=10. VTA GABA to VP iLTP: $p<0.000$, ANOVA, n=5, iLTD: $p<0.0001$, ANOVA, n=5). Alternatively, plasticity could also be determined by cell subtype. Preliminary single cell PCR data revealing subtypes of recorded VTA GABA cells suggests that variable plasticity can potentially be explained by circuit dynamics and subtype classification. Our study illustrates VTA GABA cells innervating DA cells may facilitate increased dopamine release via iLTP, and GABA neurons innervating the NAc and LHb could modulate reward/aversion through iLTP while VTA GABA cells innervating the VP have a more nuanced role in the reward circuit.

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Title: Emergence of Dorsal Striatal Decision Signals Across Repeated Trial-and-Error Learning

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Abstract: Adaptive decision-making requires inferring the latent rule that links actions to outcomes. Early choices are often exploratory, whereas accumulated experience supports efficient, expert performance. The striatum is implicated in representing decision variables and guiding reward-based action selection. Although prior work shows that striatal activity evolves

as animals acquire static procedural rules, it is unclear how decision-related signals emerge during novice trial-and-error learning and transition to stable expert representations. Given evidence that dorsomedial striatum (DMS) and dorsolateral striatum (DLS) differentially support goal-directed and habitual control, respectively, we hypothesized that DMS activity would be preferentially engaged during early trial-and-error rule acquisition, whereas DLS activity would become more prominent with repeated training. To test this, we implanted four 120-channel probes, two in DMS, two in DLS (480 channels total, 240 per region), and recorded neural activity in rats from the first day of a probabilistic reversal-learning (PRL) task through 12 days of training. In the present analysis, we focused on the first three sessions from four male rats and recorded 1,370 units (608 DMS, 762 DLS). Spikes were aligned to task events (trial onset, trial initiation, lever extension, lever press, and outcome delivery), and multivariate regression models were used to quantify encoding of current choice, outcome, and their interaction. We observed a robust increase in the fraction of choice-modulated neurons around lever press, rising from 14.4% to 64.2% in DMS and from 33.1% to 62.6% in DLS between sessions 1 and 3. Outcome encoding following outcome delivery also increased across training, from 8.7% to 33.3% in DMS and from 21.9% to 36.8% in DLS. Notably, mixed-effects logistic regression models showed that both DMS and DLS exhibited highly similar temporal trajectories in the evolution of these encoding patterns over early training. Thus, in contrast to our hypothesis, DLS is actively engaged from the beginning of training in a PRL task in which action-outcome contingencies require continuous updating. Overall, these findings suggest that DMS and DLS are dynamically reorganized during early reversal learning, with more similar functional evolution than predicted by a strict goal-directed versus habitual dissociation.

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Nanosymposium

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: Clamping dopamine release in vivo reveals critical functions in learning and movement

Authors: *S. LI[1], P. CAPELLI[2], A. MAROPAKIS[3], C. MUSUMECI[3], G. KNIPE[3], B. L. SABATINI[4];
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Abstract: Neuromodulator signals are correlated with learning and motivation, but causal tests require manipulating their timing, amplitude, and location with high precision. We developed BrainClamp, a closed-loop interface that stabilizes dopamine (DA) signals or imposes user-defined DA trajectories in behaving mice. Our results showed that BrainClamp is able to remove spontaneous and event-evoked DA fluctuations in a region-specific manner. Clamping DA or replaying DA trajectories differentially affects learning at distinct stages. Therefore, BrainClamp opens an valuable new avenue for detailed causal testing of neuromodulator function in vivo.

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Topic: H.02. Reward and Appetitive Learning and Memory

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NIH Grant R01 MH120131

Title: Dopaminergic signatures of "state" and "trait-like" pessimism in mice

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Abstract: Mesolimbic dopaminergic neurons support the learning of reward expectations. Although reward expectations reflect objective reward probabilities, they are also influenced by variation within and between individuals. This variation can take the form of pessimistic bias, as in mood disorders, yet its relationship to dopaminergic signaling is unclear. Here, we use a Pavlovian task in mice that provides a continuous behavioral measure of reward expectation during ambiguity while recording the activity of dopaminergic projections to the nucleus accumbens. Subjective, trial-to-trial ("state") pessimism was associated with decreased dopaminergic activity during ambiguous cues and compensatory increased reward consumption and decreased reward omission signals. In contrast, decreased cue-evoked activity was combined with amplified reward omission signaling in mice with pessimistically skewed cue interpretation ("trait-like" pessimism). Thus, state pessimism engages homeostatic updating to buffer negative outcomes and amplify positive ones, whereas trait-like pessimism is associated with larger reward omission signals that may sustain pessimistic bias.

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Title: Broadly-projecting mesolimbic dopamine neurons implement a distributional critic across the striatum

Authors: *S. MATIAS[1], C. RULLÁN[6], M. G. CAMPBELL[2], A. S. LOWET[7], S. XU[8], X. LU[9], Y. WU[1], R. SCHALEK[1], J. W. LICHTMAN[1], M. WATABE-UCHIDA[3], J. DRUGOWITSCH[4], N. UCHIDA[5];
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Abstract: Animal behavior relies on the coordinated action of multiple learning systems in the brain. One of these systems, the basal ganglia, implements a reinforcement learning (RL) algorithm in which dopamine (DA) neurons signal reward prediction errors (RPEs), the difference between actual and expected rewards, to drive value learning through cortico-striatal plasticity. Recent work has revealed two advances. First, DA neurons can encode entire reward distributions, rather than only mean reward values, consistent with distributional reinforcement learning, a framework used in modern artificial intelligence. Second, DA projections to different striatal regions exhibit functional heterogeneity, suggesting that not all DA neurons encode canonical RPEs. To investigate the anatomical and functional organization of DA signals across the striatum, we performed multi-fiber photometry recordings of DA axons throughout the striatum, with recording locations verified using micro-computed tomography. Across tasks involving reward and punishment, signals consistent with positive RPEs were observed throughout the striatum, although their magnitude varied across regions. In contrast, signals consistent with negative RPEs were restricted to the ventral striatum and rostral dorsal striatum (DS), revealing a rostro-caudal gradient in RPE coding. Because fiber photometry cannot resolve functionally distinct axons within a recording site, we next performed projection-identified electrophysiological recordings of midbrain DA neurons. We found that canonical RPE-encoding neurons project not only to the lateral nucleus accumbens (lNAc) but also to DS

regions. These broadly-projecting DA neurons, together with lNAc-projecting neurons, exhibited structured heterogeneity predicted by distributional RL, including both optimistic and pessimistic representations of reward distributions, which were absent in DA neurons projecting exclusively to DS. Optimistic and pessimistic neurons coexisted within an individual animal and were organized along a spatial gradient of optimism within the ventral tegmental area. These findings identify a population of broadly-projecting DA neurons that broadcasts distributional prediction errors across both ventral and DS territories. This architecture provides a neural substrate for associative learning while supporting continuous action control. More broadly, our results establish new links between biological and artificial intelligence and raise fundamental questions about how value and action representations are integrated to support flexible decision-making and behavioral control.

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: Selective Deletion of a Glutamate transporter, EAAT3, in Dopaminergic Neurons Disrupts Amphetamine Induced Dopamine Signaling

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Abstract: Excitatory amino acid transporter 3 (EAAT3) is a neuronal glutamate transporter that plays a critical role in glutamatergic neurotransmission and is implicated in multiple neuropsychiatric disorders. However, its role in ventral tegmental area (VTA) dopaminergic circuits remains to be elucidated. To address this question, we generated mice with selective deletion of EAAT3 in tyrosine hydroxylase expressing neurons (TH-EAAT3 KO). Using in vivo fiber photometry in freely moving mice, we monitored VTA dopaminergic neuronal activity using a genetically-encoded calcium sensor in response to systemic amphetamine (AMPH) administration and measured AMPH-evoked dopamine release in the nucleus accumbens (NAc) using dLight. Behavioral responses to AMPH were assessed by locomotor activity. To directly

assess dopamine release capacity independent of systemic drug effects, dopaminergic terminals were optogenetically stimulated, and evoked dopamine transients were quantified with dLight photometry.
Results showed that control mice exhibited robust AMPH induced locomotor activation accompanied by increased dopamine release in the NAc. Interestingly, AMPH also produced a reduction in VTA dopaminergic GCaMP activity, consistent with engagement of dopaminergic feedback mechanisms. In contrast, TH-EAAT3 KO mice displayed significantly attenuated locomotor responses and blunted AMPH evoked dopamine release. The AMPH induced decrease in VTA GCaMP activity observed in control mice was largely absent in TH-EAAT3 KO mice, indicating potential loss of negative feedback. Further, optogenetic stimulation of dopaminergic terminals evoked dopamine release was decreased in TH-EAAT3 KO mice relative to controls. Together, these findings identify EAAT3 as an important regulator of mesolimbic dopamine function and demonstrate that loss of EAAT3 alters dopamine release dynamics and VTA dopamine neuron activity in response to psychostimulants.

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Nanosymposium

NANO30: Multi-Level Mechanisms for Flexible Behavior

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Time: Tuesday, November 17, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO30.01

Topic: I.03. Decision Making

Title: Prefrontal Circuit Mechanisms Linking Emotional Context to Behavioral Choice

Authors: *A. EL AZRAOUI[1], Y. HUMEAU[2], E. HARRELL[3], C. HERRY[1];
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Abstract: Adaptive behavior requires the flexible integration of affective context into ongoing decision-making. Failures of this integration are implicated in a range of neuropsychiatric conditions, yet the underlying circuit mechanisms remain incompletely understood. The prefrontal cortex (PFC) has been broadly linked to both emotional regulation and executive function, but how these roles interact at the level of neural dynamics is unclear.
We investigated PFC population activity in mice performing a context-dependent behavioral task requiring distinct actions in response to cues associated with different motivational outcomes. Using large-scale electrophysiological recordings, we characterized how neural representations tracked task-relevant variables across conditions.
We find that PFC ensembles exhibit context-dependent dynamics that diverge across motivationally distinct states, even when sensory input and motor output are matched. At the level of individual neurons, responses were heterogeneous and carried mixed selectivity across relevant task dimensions. We also present preliminary findings on how neural representations shift under conditions of contextual uncertainty.

These results contribute to a mechanistic understanding of how the PFC supports flexible, affect-guided behavior, with implications for circuit-level models of mood and anxiety disorders.

Disclosures: A. El Azraoui: None. **Y. Humeau:** None. **E. Harrell:** None. **C. Herry:** None.

Nanosymposium

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Title: Humanizing cortical circuits with SRGAP2C expression facilitates flexible behavior and preservation of task-relevant information

Authors: *C. BRAMATI[1,2], J. RAMIREZ RUIZ[1], F. POLLEUX[3], G. DI CRISTO[2,1], B. A. EBITZ[1], R. ARAYA[1];
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Abstract: When navigating uncertain environments, animals have to integrate sensory cues to continuously adapt their behavior. This flexibility relies on updating internal predictions, and can give rise to different learning strategies, from conservative trial-and-error to exploratory behaviors that favor information accumulation. We show that the human-specific gene SLIT-ROBO Rho GTPase activating protein 2C (*SRGAP2C*) facilitates flexible strategies in mice performing a sensory detection task. *SRGAP2C* emerged from the ancestral gene *SRGAP2A*, encoding a postsynaptic protein regulating synaptic development (Dennis et al. 2012; Charrier et al. 2012). Inducing expression of *SRGAP2C* in cortical pyramidal neurons (CPNs) of mice enables the emergence of human-like features of synaptic development (Charrier et al. 2012; Fossati et al. 2016), increased cortico-cortical connectivity and improved sensory discrimination performance (Schmidt et al. 2021). To test if *SRGAP2C* expression specifically in CPNs affects perceptive behavior, we trained adult wild-type (WT) and SRGAP2C mice to learn a Go-NoGo task that involves learning to associate a whisker stimulus with the presence of a water reward. SRGAP2C mice displayed an enhanced drive to lick, a strategy that accelerates the learning of stimulus-reward associations at the cost of more punishment timeouts. Importantly, we confirm

that licking is contigent on sensory evidence rather than compulsive for both groups. We further show that SRGAP2C mice gather more task-related information in early sessions and their behavior is more structured with respect to the sensory input later in training, indicating enhanced preservation of task-related information. In addition, reinforcement learning simulations show that increasing representational capacity replicates key features of SRGAP2C mice's behavior. These results reveal that the induction of human-specific SRGAP2C expression drives a shift in learning strategy, favoring information accumulation and an improved use of perception to guide action. This suggests that evolutionary changes in cortical connectivity induced by SRGAP2C may have contributed to the emergence of distinct features of human learning and flexible decision-making.

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Support: NIH NS126143

Title: What writes the rhythm? Gene networks underlying memory relevant oscillations in ex vivo human cortex

Authors: *A. FREELIN[1], H. MOORE[2], M. DEHNAD[2], C. CALOVICH-BENNE[2], E. HUANG[1], K. WEI[1], M. WELLS[1], B. C. LEGA[3], G. KONOPKA[1];
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Abstract: The brain's ability to encode stable representations of experience over time is the foundation of episodic memory. This defining feature of human cognition requires precise temporal integration of neuronal activity across cortical networks. The temporal cortex is a critical hub, with intrinsic oscillatory dynamics implicated in memory processes. While neural oscillations are conserved across species, oscillations found in the human temporal lobe are thought to exhibit distinct, functional properties related to human behavior and cognition. Notably, human theta range oscillations occur at comparatively lower frequencies, and evidence suggests functional heterogeneity within human theta range. Slower theta oscillations are specifically implicated in episodic memory encoding and depend on cholinergic modulation via muscarinic receptor signaling. These oscillations act as a window into collective and precisely coordinated network activity, however, the cell-type specific gene networks that enable cells to participate in coordinated oscillatory dynamics remain unknown.
To address this, we utilize live, cultured human temporal cortex. Here, we use carbachol, a cholinergic agonist, to recapitulate memory encoding network dynamics seen in humans.

Microelectrode array recordings are paired with spatial transcriptomics and multiomics following carbachol application. This design allows direct comparison of oscillatory dynamics and gene expression following enhanced cholinergic activity. We find that cholinergic induction of slow oscillations in *ex vivo* cortical tissue engages memory relevant gene networks, implicating distinct transcriptional programs underlying this oscillatory activity. Our results highlight a novel framework for identifying gene level contributors to memory-relevant neural dynamics in the human cortex.

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Title: Identifying Cognitive Strategies of Freely-Moving Mice Hunting in a Complex Environment

Authors: *L.-Q. ZHANG, N. SHETTIGAR, J. TERAN, K. BRANSON, E. J. DENNIS; HHMI Janelia Res. Campus, Ashburn, VA

Abstract: To study decision-making in mice, we typically design highly controlled tasks in simplified environments to isolate a single computation. However, even in these settings, animal behavior can often be composed of distinct states that involve different cognitive processes (e.g., Ashwood et al., 2022; Bruijns et al., 2025). We are interested in studying neural computations within natural behavior, where decisions are self-directed by the animal and not restricted to stereotyped movements. In particular, we ask freely-moving mice to hunt for crickets in a large (~2 x 2 m) hexagonal maze containing 157 tiles. Sixteen of these tiles contain speakers and hidden cricket-release sites, only one of which serves as the target at any given moment. As the animal moves around, a real-time system tracks the mouse's location. Mice can gain information about the target location by staying still for more than 0.5 seconds, which triggers a sound played through a speaker in the target tile. If the animal enters and waits inside the target tile, a trap door opens and releases a live cricket reward. After each successful capture, a different cricket tile becomes the target. Mice quickly learn this task, achieving peak performance of 4 - 8 captures per 1-hour session. This task creates rich, self-directed behavior while also introducing substantial variability, which raises the challenge of identifying when the animal is engaged in different computations. To address this, we integrate high-resolution pose tracking, locomotion analysis, and search strategy modeling to segment behavior. We identify distinct behavioral

states, including exploration, sound-driven hunting, and disengagement. Each of these states is marked by a characteristic combination of pose, movement, and spatial search patterns. In particular, we identify a high-efficiency search strategy during which mice integrate auditory cues across multiple locations in space. Our results suggest that behavioral segmentation with multimodal data provides a useful framework for studying decision-making in natural behaviors.

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Title: Temporal-orbitofrontal pathway regulates choices across physical reward and visual novelty

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Abstract: Expectation of novel visual stimuli impacts how we evaluate primary rewards and make decisions. This is the case even when novelty itself is non-instrumental - i.e., when it does not contribute to reward rates or facilitate new learning. Although such interaction between non-instrumental preference for novelty and the valuation of physical rewards is crucial for adaptive decision-making, its neural mechanisms remain unclear. Here, we identify a temporal-orbital neural pathway that regulates this novelty-reward interaction during decision-making. The

pathway comprises perirhinal cortex (PRh), a final stage of the ventral visual system involved in novelty detection and prediction, and orbitofrontal cortex (OFC), which receives dense PRh inputs and is known to signal the reward values associated with visual stimuli. We trained monkeys on a task with several contexts. In the first context, five visual offers predicted future novel versus familiar objects with five distinct probabilities (% of novel/familiar objects: 0/100, 25/75, 50/50, 75/25, 100/0). Obtaining novel objects predicted large rewards, while obtaining familiar objects predicted small rewards. Conversely, in a second context, five other offers also predicted novel objects with the same five probabilities, but here, novel objects predicted small rewards instead of big rewards, while familiar objects predicted big rewards rather than small rewards. Hence, in the first context, novel objects had a high reward value, while in the second, they had a low reward value. When choosing among these offers, animals consistently preferred those with high expected reward and high expected novelty over those with high expected reward and low expected novelty, indicating that expected novelty boosted reward valuation. This novelty-reward interaction was reflected in neural activity in both OFC and PRh. Novelty-expectation signals emerged earlier and were more prominent in PRh, whereas a neural signal more closely aligned with subjects' preferences for the offers was more prominent in OFC, suggesting that PRh could broadcast novelty-expectation signals to OFC and OFC is more closely tied to integrating novelty signals and reward to guide behaviors. To test this, we injected an AAV vector expressing hM4Di into PRh and performed a projection-specific chemogenetic disruption of PRh-OFC pathway by locally injecting DCZ into OFC where hM4Di was expressed on PRh axons. This manipulation altered the impact of expected novelty on reward valuation. Our data suggest that the ventral visual system contributes to novelty-reward interactions during valuation through direct projections to prefrontal cortex.

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Title: Representations of the intrinsic value of information in mouse orbitofrontal cortex

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Abstract: Animals are motivated to acquire knowledge, often seeking information that reduces uncertainty about future events even when it yields no extrinsic reward. This implies that information has intrinsic value. We developed an information seeking task for mice to investigate neural representations of the value of information about the receipt of reward or punishment. In task sessions in which mice chose whether to receive information about water reward, mice strongly preferred to receive information versus no information (information preference 78%, $p<0.001$, N=36 mice). Moreover, mice sacrificed water to pay for information, preferring to receive information even when it decreased their water reward. However, the preference to receive information predicting aversive mild electric shock was weaker and more variable across animals (information preference 61%, $p=0.058$, N=21 mice). Thus, mice behave as if information has intrinsic value, with information about reward valued more highly than information about punishment. We recorded activity in orbitofrontal cortex (OFC) using one-photon calcium imaging through a microendoscope. In reward sessions (N=7 mice, 1138 cells), we observed a representation of the predicted value of information that scaled with the duration of uncertainty. Linear classification and population geometry analysis revealed that this representation was orthogonal to the OFC representation of predicted water reward value (angle between information and water value modes=99.9 degrees). Preliminary recordings identified cells encoding the prediction of information about shock, and our current analyses aim to determine the relationship between this activity and the representation of the value of information about reward. We optogenetically inactivated OFC during the presentation of information-predicting odor cues, and preliminary data suggest that OFC is causally involved in the preference for information. These results indicate that OFC represents the value of information about both rewards and punishments and that OFC activity at the moment of information prediction contributes to seeking information about uncertain future events.

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Title: Individual differences in neural representations of rule states in a Set Shift task

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Abstract: Cognitive flexibility is a key executive function, and can be defined as the ability to adaptively shift between choices or strategies based on environmental feedback. Maladaptive cognitive flexibility has been implicated in numerous neuropsychiatric conditions. Understanding drivers of altered cognitive flexibility between individuals can thus be poised to reveal mechanisms of neuropsychiatric risk and resilience. We demonstrate a newly-developed operant touchscreen Set Shift task that permits robust and continuous testing in mice, and use this task to interrogate individual differences in the computations supporting cognitive flexibility. This task requires animals to both commit to a rule-specific choice during periods of relative certainty (stable rule responding) and to flexibly explore alternative options during periods of uncertainty (rule shifts). Animals occupy different cognitive states as they navigate the unsignaled changes in this environment--exploiting the current rule state and exploring to learn the new rule state following a rule shift. During Set Shift, we discovered that female mice completed significantly more rule shifts with fewer errors than males. Following rule shifts, female mice learn the new rule faster and transition to exploiting the new rule state sooner compared to males. To investigate the neural bases of sex-biased individual differences in cognitive flexibility, we are using free-moving in-vivo electrophysiology, recording medial prefrontal cortex (mPFC) neural activity across sexes and performance levels during the Set Shift task. Current analyses are investigating how neural representations differ across individuals. Thus far, we have identified distinct neural ensemble representations of state, outcome, and choice in mPFC activity. In particular, explore and exploit states can be differentially decoded, and we find state-based differences in neural synchrony aligned to rule shifts. Current analysis suggests that efficient transitions between explore and exploit states (and rule shifts) are related to features of these ensemble representations. Our preliminary data presents evidence that individual differences in Set Shift performance are related to the quality of neural representations of rule states between individuals.

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Title: Learnability and Reward Prediction Error in Dorsal Anterior Cingulate Cortex

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Abstract: Humans and animals adapt to their environments by learning predictable relationships between stimuli and outcomes. However, in natural settings such learnable associations are often intermixed with coincidental juxtapositions that are random and unlearnable. An ability to distinguish learnable from unlearnable patterns may contribute to an efficient allocation of cognitive effort. However, it is unknown whether or how the brain detects and encodes learnability. To investigate this, we trained two adult macaque monkeys to perform a standard 5-item dual-list transitive inference task using pictorial stimuli drawn at random from a large image set. We modified this task to present two pictorial sets randomly interleaved within a single behavioral session. One set was "learnable," meaning that the stimuli were implicitly ordered and monkeys were rewarded for choosing the higher-rank stimulus. The other set was "unlearnable" such that stimuli were unordered and monkeys were rewarded probabilistically, independent of their choices, with reward rates matching those in the learnable set. Monkeys were able to successfully inferred the correct stimulus order for learnable sets. Surprisingly, they often made highly consistent choices for the unlearnable set, as if they detected a subjective ordering that did not exist. The strength of this subjective ordering varied from session to session, providing an opportunity to study the neural basis of learnability through neural recording and neural network simulations. We recorded neurons in the dorsal anterior cingulate cortex (dACC, area 24c, N=1072) using linear arrays. As a population, dACC neurons tended to respond before and after the monkeys' choices and after reward delivery. Single-unit and population responses encoded the outcome (reward/no reward) as well as learnability and the magnitude of prediction errors, with the latter two variables being significantly correlated with the magnitude of the behavioral distinction between learnable and unlearnable sets. We also tested the performance of recurrent neural network models with neuromodulator-dependent Hebbian plasticity. We found that such networks successfully recapitulated our behavior findings. Our results suggest a role for reward prediction error in dACC in monitoring learnable vs. unlearnable reinforcement, possibly by regulating Hebbian plasticity. These results contribute to a deeper understanding of the mechanisms that control learning in complex natural settings.

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Nanosymposium

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Title: Stimulus similarities modulate novelty computation in naturalistic environments

Authors: *S. BECKER[1], A. MODIRSHANECHI[2], W. GERSTNER[1];
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Abstract: How does the brain compute novelty when new experiences resemble familiar ones? Although novelty signals are well established as drivers of exploration and learning, existing computational models largely overlook the role of stimulus similarities, a factor that is pervasive in real-world environments, where sensory inputs are high-dimensional and continuously varying. We address this gap with a biologically plausible model in which generalization between similar stimuli modulates novelty signals and shapes novelty-driven behavior. We validate our computational framework on two publicly available datasets. First, we demonstrate that generalization across visually similar stimuli systematically shapes novelty responses in mouse visual cortex. Second, we show that generalization across nearby spatial locations governs how mice explore an unfamiliar environment. Beyond fitting existing data, our model generates mechanistic predictions about the synaptic plasticity rules operating in novelty-computing circuits, and allows for theory-driven experiment design. We illustrate the latter by developing an experimental protocol that systematizes the study of similarity effects on novelty computation in the brain. Lastly, we leverage our model to disentangle the impact of stimulus similarities from well-described effects of temporal stimulus sequence and neural integration timescales on novelty detection. We derive a conceptual framework that characterizes novelty computation in naturalistic environments along two complementary axes: a temporal axis, capturing interactions of temporal stimulus sequence with neural timescales, and a similarity axis, describing the effects of stimulus similarities as perceived by underlying neural representations.

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Title: Prefrontal Representations of Structured Meaning: From Single Neurons to Cross-Species Codes

Authors: *M. JAMALI[1], S. LEE[1], B. MASH[2], I. CAPRARA[1], R. BÁEZ-MENDOZA[3], Z. WILLIAMS[1];
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Abstract: Flexible behavior depends on the ability to extract and represent structured meaning from complex sensory input. While traditional models of neural computation have emphasized stimulus-response mappings and reward-based learning, how structured semantic information is encoded in neural circuits and how these representations support adaptive behavior across contexts and species remains poorly understood.
From sequences of speech sounds or letters, humans can extract rich and nuanced meaning through language, yet how linguistic meaning is derived in neural tissue at the level of single cells and action potential timescales remains largely unknown. Here, we present a broad framework for studying semantic representations in the prefrontal cortex across humans and non-human primates, linking single-neuron coding, columnar organization, and cross-species comparisons. In humans, we combine ultra-high-resolution Neuropixels recordings with naturalistic and structured speech paradigms to examine how cortical microcircuits support speech perception and production. We find that prefrontal neurons encode semantically informative structure in a context-dependent manner, with depth-specific dynamics across cortical depth and distinct activity patterns during receptive versus expressive language use. Extending this framework, we investigate whether analogous semantic representations are present across species. Using homologous prefrontal regions in humans and rhesus macaques, we record single-unit activity during passive viewing of image sequences designed to probe structured semantic organization. Stimuli are embedded in high-level semantic and low-level visual feature spaces, enabling separation of conceptual versus perceptual contributions to neural responses. Across both species, individual neurons exhibit selective and decodable responses in high-level semantic space, while population-level analyses reveal partially shared representational structure alongside species-specific organization.
Together, these findings suggest that the prefrontal cortex supports a conserved yet flexible neural architecture for representing structured meaning across modalities and species. This work provides a comparative framework for understanding how semantic structure is implemented in neural circuits and how such representations may support adaptive, context-sensitive behavior beyond simple stimulus-driven or reward-based accounts.

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Title: Distinct mesocortical dopamine pathways differentially encode behavioral features of cognitive flexibility

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Abstract: Cognitive flexibility enables adaptive decision-making in changing environments and relies on coordinated activity across distributed cortical networks. The medial prefrontal cortex (mPFC) and anterior insular cortex (aIC) are key components of this network and receive dense dopaminergic innervation that is critical for cognition and behavioral adaptation. However, whether distinct mesocortical dopamine circuits contribute differentially to specific aspects of cognitive flexibility remains unclear. Using projection-specific viral tracing in mice, we found that the mPFC and aIC are innervated predominantly by non-overlapping populations of midbrain dopamine neurons. To examine the functional dynamics of these pathways, we performed dual-site fiber photometry to simultaneously monitor dopamine signaling in the mPFC and aIC during an attentional set-shifting task (AST). In the habituation phase, food intake induced robust and sustained dopamine release in both regions. In contrast, mesocortical dopamine dynamics diverged during the task phase. As animals progressed through successive trials, mPFC dopamine responses became increasingly associated with rewarded approaches, whereas aIC dopamine responses were preferentially enhanced during nonrewarded approaches. In addition, dopamine activity in both pathways was modulated by prior outcomes and task history, suggesting that mesocortical dopamine signaling integrates information across multiple timescales to influence subsequent learning and choice behavior. Ongoing studies are testing the causal contributions of these pathways using projection-specific optogenetic manipulations during set-shifting. Together, these findings demonstrate that anatomically distinct mesocortical dopamine circuits encode complementary behavioral features during flexible decision-making. These results provide new insight into how projection-specific dopamine signaling supports cognitive flexibility and adaptive behavior.

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Department of Intelligent Precision Healthcare, Sungkyunkwan University

Title: Neurocomputational dynamics of flexible goal switching during adaptive planning

Authors: *S. PARK[1], H. CHOI[2], S. GO[3], Y. JEONG[4], W. SHIM[3];
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Abstract: The ability to flexibly update plans and goals in response to environmental changes is central to adaptive decision-making in humans. However, most previous studies have relied on static environments, single-goal settings, or simplified decision-making paradigms that fail to capture the dynamic and partially unobservable nature of adaptive planning under changing task demands. To address this, we developed a novel task and modeling framework that uses eye-tracking data to reconstruct internal planning processes underlying adaptive goal switching. In our task, participants (N=54) generated mathematical equations using presented numbers and operators to reach one of two target numbers, then executed their plans while flexibly updating their target in response to changes in available numbers. We reconstructed their internal planning and predicted real-time goal switching using a Bayesian framework that continuously updated priors for the targets based on the likelihood of fixated items relative to each target. This framework allowed us to estimate moment-by-moment goal-switching probabilities and capture individual differences in uncertainty and learning rates, which reflect the precision of likelihood computation and the speed of belief updating, respectively. Behaviorally, better task performance was associated with lower uncertainty and higher learning rates, particularly when initial plans became infeasible. At the neural level, model-derived goal-switching probabilities explained activity in reward processing and valuation networks, including the dorsal anterior cingulate cortex (dACC), nucleus accumbens (NAcc), and caudate nucleus. Critically, functional connectivity between the dACC and caudate increased specifically when participants needed to rebuild a new plan, and stronger connectivity was associated with lower uncertainty and better task performance. Furthermore, multivariate pattern similarities in reward-related regions reflected similarities across participant-specific model parameters, with dACC representations selectively aligned among high performers during plan rebuilding. Together, these findings show that an eye-tracking-based Bayesian framework can capture behavioral and neural signatures of adaptive goal switching, highlighting the role of a dACC-striatal network in flexibly updating goal utilities under uncertainty.

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Marine Biological Association Peter Baker Investigatorship

Title: Exploring subjective information value in a cephalopod

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Abstract: Like humans, a range of mammalian and avian species seek advance information about uncertain future events, even though the information cannot be used to improve reward outcomes and is often costly, a phenomenon frequently referred to as 'paradoxical choice'. In the task, subjects prefer an alternative that provides prospective information about delayed, stochastic reward outcomes (reward/no reward), over one that does not. These intriguing preferences highlight that non-human animals ascribe subjective value to informative stimuli and may possess at least rudimentary forms of curiosity. However the underlying cognitive mechanisms, function, and evolutionary origins of non-instrumental information-seeking behaviour is unclear. To address this, we have adapted the paradoxical choice paradigm to investigate curiosity-motivated decision-making in a cephalopod for the first time, the common cuttlefish, *Sepia officinalis.* Automated behavioural testing and task control were be implemented using a new platform we have developed that facilitates closed-loop cognitive experiments on aquatic species. We present data showing that cuttlefish can be trained to self-initiate choice trials in a closed-loop experimental set-up that uses real-time video tracking. Unlike with mammals and birds, we found no evidence that cuttlefish ascribe subjective value to non-instrumental prospective information. These remarkably intelligent cephalopods display episodic-like memory and can take prospective actions for the future. We argue that because cuttlefish evolved advanced intelligence independently from vertebrates, with divergent socio-ecological pressures shaping their cognitive evolution, they offer a unique opportunity to further extend our understanding of the cognitive substrates and socioecological factors that promote curiosity-like behaviour.

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Title: Ultrastructural preservation of a whole large mammal brain with a protocol compatible with human physician-assisted death

Authors: A. SONG, A. LAVERGNE, ***B. WROBEL**;
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Abstract: A high-fidelity computational model of a whole human brain will require preservation of the ultrastructure at the level of the entire organ, post-mortem. For such a model to reflect as closely as possible the brain in the living state, artifacts that arise during both the agonal phase and the postmortem interval will need to be minimized. This is potentially feasible if a terminally-ill patient donates their brain for research following physician-assisted death. Here, we modify a protocol for aldehyde-stabilized cryopreservation to make it compatible with physician-assisted death. We used pigs as a model, which resemble humans in cardiovascular and brain anatomy. Aldehyde-stabilized cryopreservation was designed to provide superior structural preservation of brains of any size, across all anatomical scales, compatible with diverse analytical assays and long-term storage without ultrastructural degradation. We demonstrate, with light microscopy and volume electron microscopy, that our brain preservation protocol results in connectomically traceable whole brains and propose an economically feasible storage modality that is expected to maintain stability of ultrastructure and macromolecules in the brain even for thousands of years. Most importantly, we establish that 14 min is the approximate length of the perfusability window—the time after the cardiac arrest during which blood washout needs to be initiated so that the brain ultrastructure is preserved.
(doi:10.64898/2026.03.04.709724)

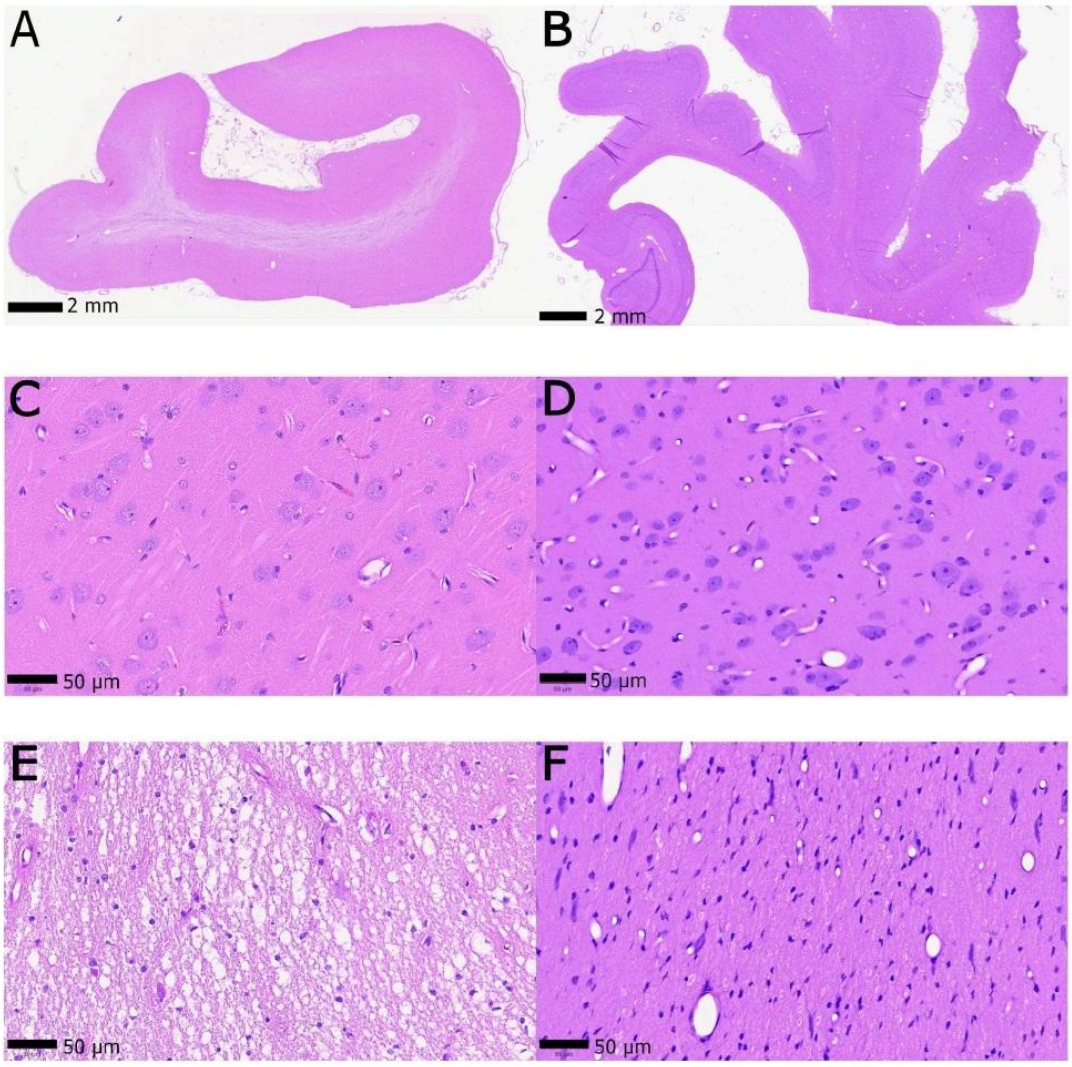


Fig 1. Distorted vs non-distorted morphology in the preserved porcine brains. A visibly lighter region of hematoxylin and eosin staining (pallor; panel A) in the neocortex from the right hemisphere from an imperfectly-preserved porcine brain indicates distorted morphology. Higher power images reveal erythrocytes in capillaries in the gray matter (C) and the appearance of vacuolation in the white matter (E). No distorted morphology is observed in the neocortex from the right hemisphere a well-preserved porcine brain—pallor is absent (panel B). Higher magnification shows empty capillaries in the gray matter (D) and no vacuolation in the white matter (F).

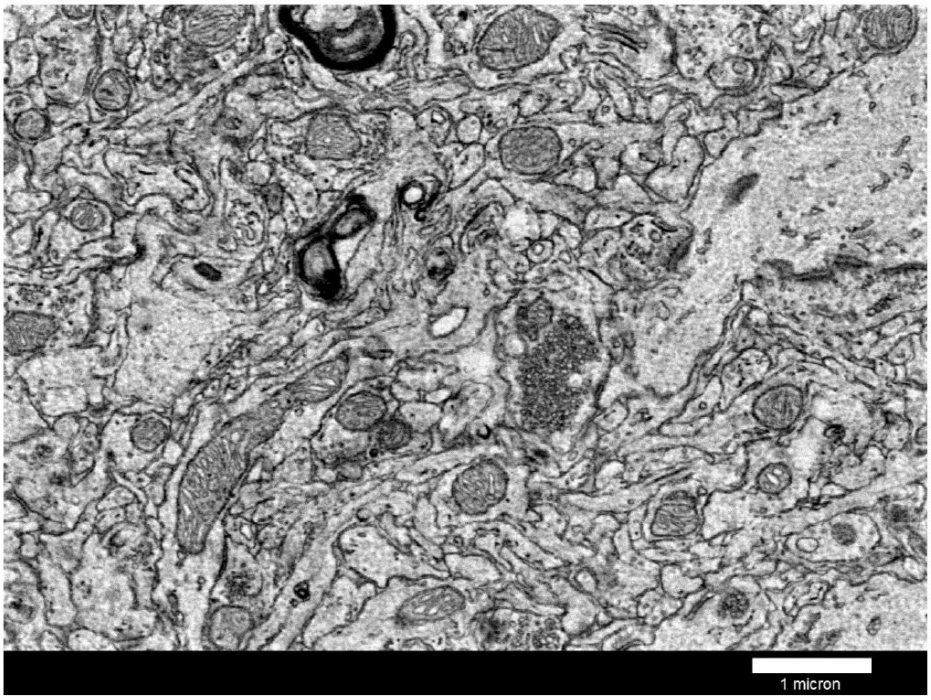


Fig. 2. First section in a wafer-SEM stack of the neuropil from a randomly chosen area in the occipital lobe of a well-preserved porcine brain. All processes appear well preserved and traceable throughout the stack. The stack was obtained by Ken Hayworth at Janelia Research Campus. Used with permission.

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HHMI

Title: The brain and nerve cord connectome reveals distributed, body-wide control circuits in adult Drosophila

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Abstract: From the processing of sensory input to the control of motor output, behavior requires coordinated signaling across the nervous system. Large-scale, comprehensive wiring diagrams that describe the connections between individual neurons at synaptic resolution — "connectomes" — provide a critical resource for identifying and understanding these neuronal circuits. For the key model organism *Drosophila melanogaster*, multiple connectomes have been generated and have provided important insight into the function of the visual system, navigational circuitry, nerve cord (the analogue of the vertebrate spinal cord), and more. However, these connectomes have been of either the brain or the nerve cord, severing the descending and ascending neurons that pass through the neck to connect these nervous system regions and that are essential for the sensorimotor transformations that underlie behavior. Here, we report the Brain And Nerve Cord (BANC), a densely reconstructed connectome of an adult female fly that spans both the brain and nerve cord. This publicly accessible resource contains the reconstructions of over 150,000 neurons as well as synapses with neurotransmitter predictions, nuclei, and mitochondria. We provide a hierarchy of annotations for each cell, including cell type-level labels for over 90% of the neurons. Furthermore, to "embody" this connectome, we focused particularly on the sensory and efferent neurons linking the central nervous system with the periphery and, based on comparisons with the literature, provide detailed annotations of targeted body parts and functions. Using the BANC, we show that efferent neurons are primarily influenced by sensory neurons in the same body part, forming local feedback loops. Long-range circuits involving ascending and descending neurons then link these local loops, and thus multiple body parts. Ascending and descending neurons can be clustered into broad behavioral groups, in which individual neurons mediate distinct but related sensorimotor transformations, suggesting a modular organization. Overall, we find a central

nervous system architecture that is distributed, parallelized, and embodied, similar to distributed control architectures in engineered systems.

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Nanosymposium

NANO31: Connectomics

Location: WCC Rm 145

Time: Tuesday, November 17, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO31.03

Topic: J.03. Anatomical Methods

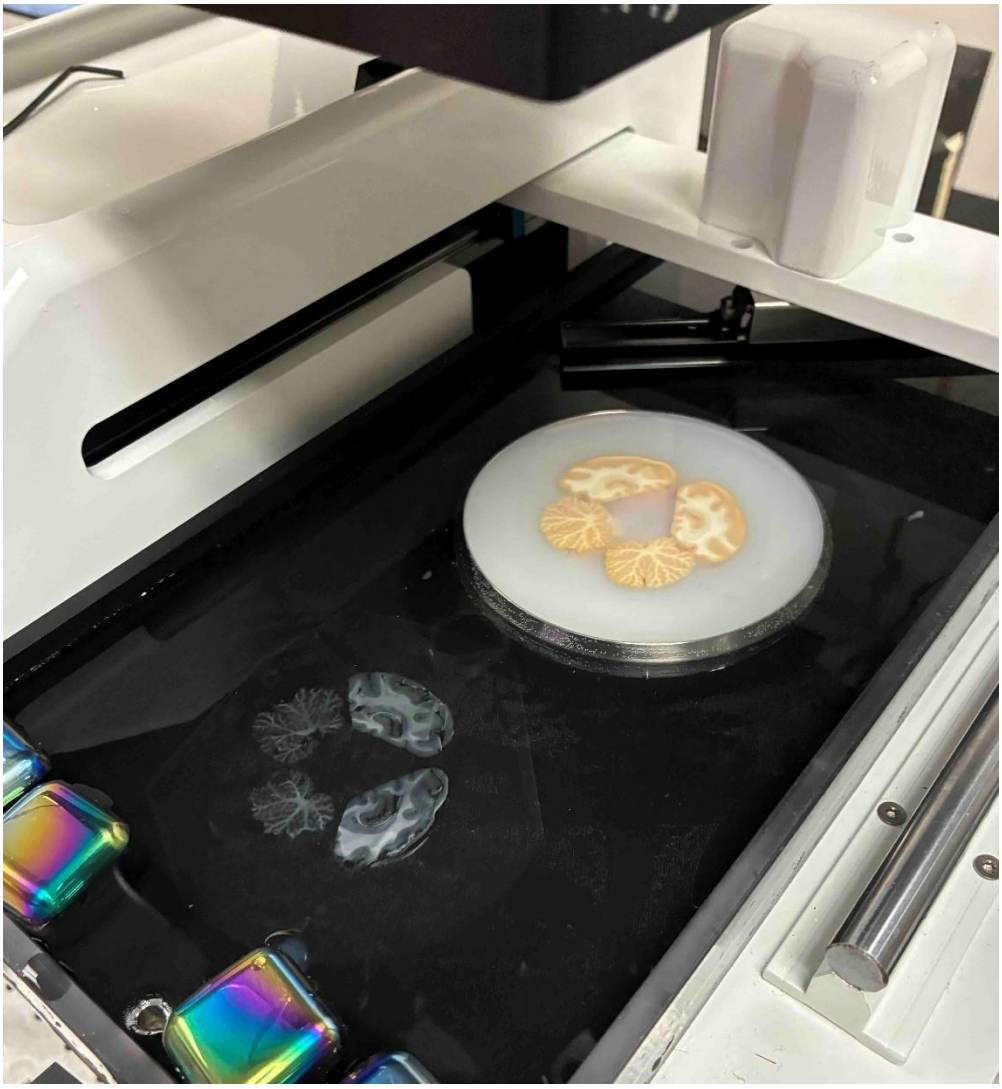
Support: KAKENHI-PROJECT-17K13275
KAKENHI-PROJECT-15H06872
5R01MH126923-05

Title: Compresstome-enabled preservation of neuronal morphology in non-human primate brain tissue for histological and molecular analyses

Authors: A. FUJIMOTO[1], S. H. FUJIMOTO[3], M. YEATTS[2], T. AKKIN[2], ***A. CHU**[4];
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Abstract: Non-human primates (NHP) provide an important translational bridge between rodent models and human neuroscience. Conventional histological workflows for large tissue samples, such as NHP brains, often rely on cryosectioning, which may introduce freezing artifacts that alter tissue morphology and compromise downstream analyses. We evaluated a fixed-tissue, non-frozen-sectioning workflow using a large-diameter Compresstome vibrating microtome (VF-800-0Z) to preserve tissue architecture and cellular morphology in NHP brain specimens. Macaque brain tissue was obtained following perfusion and maintained under refrigerated

conditions prior to sectioning. Samples of the visual cortex and cerebellum were embedded in 3% agarose and sectioned at 50 µm thickness using previously obtained optimized oscillation and speed parameters. Brain sections subsequently underwent immunofluorescence imaging and qualitative assessment of tissue integrity. Uniform sections with smooth cutting surfaces that preserved cytoarchitecture across both cortical and cerebellar regions were generated. Removal of pia and surface vasculature prior to embedding further improved section quality and tissue handling from initial sectioning tests. Preliminary immunofluorescence studies demonstrate successful labeling and visualization of cellular structures, while avoiding freezing artifacts. These findings establish a practical workflow for utilizing a large Compresstome to preserve cellular morphology in translational neuroscience studies.



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Presentation Number: NANO31.04

Topic: J.03. Anatomical Methods

Support: R01MH126923
UM1NS132207

Title: Label-Free Optical Imaging of Deep Brain Stimulation Circuits in the Macaque Brain

Authors: *B. BARADARAN[1], M. YEATTS[1], N. CHINTHALAPATI[1], A. NISHIMWE[1], H. HEINKS[1], E. LIAO[1], M. D. JOHNSON[1], S. R. HEILBRONNER[2], T. AKKIN[1];
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Abstract: Anatomical connectivity is fundamental to understanding brain function and to optimizing neuromodulation therapies. This is especially critical for deep brain stimulation (DBS), where therapeutic efficacy relies on precise targeting of small, anatomically distinct populations of axons and neuronal cell bodies. Current neuroimaging modalities suffer from low spatial resolution (e.g., diffusion MRI), are limited to small tissue volumes (e.g., electron microscopy), or do not apply to the human brain (e.g., histological tracing methods). Serial Optical Coherence Scanning (SOCS) resolves these limitations by enabling large-scale, label-free volumetric brain imaging at high spatial resolution. SOCS integrates polarization-sensitive optical coherence tomography (PS-OCT) with a tissue slicer to enable three-dimensional reconstruction of brain tissue while providing multiple optical contrasts. Retardance contrast delineates myelinated fiber bundles, optic axis orientation reveals fiber trajectory alignment, and conventional OCT-derived reflectivity and attenuation provide complementary information about gray matter microstructure. We developed two SOCS systems that operate at two distinct spectral bands: near-infrared and visible light. The axial resolution is 5.5 μm and 1.5 μm, respectively, and the lateral resolution is ~10 μm. We imaged the midbrain region of two macaque brains coronally: one with the near-infrared SOCS and the other with the visible-light SOCS. An additional macaque brain that had been implanted with a DBS lead in the right subthalamic nucleus (STN) was imaged sagittally. The datasets were used to investigate motor and cingulate circuit connectivity involving clinically relevant DBS targets, including the thalamus, STN, and internal capsule pathways. The findings show that SOCS can be used to visualize white matter fascicles, such as in the internal capsule, and their anatomical relationships with neighboring gray matter structures, such as the STN, across large tissue volumes. The results also provide insight into intersubject variability, confirm the lead location, and highlight tissue interaction along the lead hole. White matter orientation can be estimated for future tractography and field modeling, which can enhance DBS targeting strategies and shape neuromodulation therapies.

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Nanosymposium

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Title: A synapse-resolution connectome spanning mouse medial entorhinal cortex and parasubiculum reveals layer II circuits associated with pyramidal cell clusters

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Abstract: The medial entorhinal cortex (MEC) and parasubiculum (PaS) are interconnected components of the mammalian navigation system, but the synaptic organization of their local circuits remains incompletely understood. Here, we present a synapse-resolution serial electron microscopy connectome spanning 0.6 mm^3 of mouse parahippocampal cortex, encompassing PaS, MEC, and their boundary regions across all cortical layers, with more than 40,000 reconstructed neurons. This dataset provides a structural resource for investigating cell-type-specific circuit organization within the PaS-MEC system. As a first application toward understanding MEC circuit organization, we focused on layer II of the MEC, a layer enriched in spatially tuned cell types. Targeted, human-proofread reconstruction across multiple pyramidal cell clusters revealed that layer II pyramidal neurons exhibit a pronounced directional organization, with apical dendrites extending predominantly parallel to the laminar plane and biased toward dorsolateral MEC. Within pyramidal cell clusters, we identified a core that is strongly depleted of neurites from neurons located outside the core, while retaining neurites from neurons whose somata reside within it. This external-neurite-exclusion core is nested within the soma-defined cluster and forms a nest-like microstructural architecture. Synaptic analysis further showed that neuronal position relative to this core is associated with distinct circuit motifs. Pyramidal neurons inside the core preferentially engage in recurrent inhibitory interactions mediated by chandelier and basket cells, whereas pyramidal neurons outside the core more frequently target stellate cells. Across multiple clusters, we also identified inter-cluster interactions in which pyramidal neurons project onto inhibitory neurons associated with neighboring clusters, forming a distributed inhibitory network linking spatially separated layer II microdomains. Together, these findings suggest that MEC layer II pyramidal cell clusters act as local circuit organizers that compartmentalize dendritic access, inhibitory recurrence, and communication with stellate-cell networks.

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Nanosymposium

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Time: Tuesday, November 17, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO31.06

Topic: J.03. Anatomical Methods

Support: The Hock E. Tan and K. Lisa Yang Center for Autism Research at Harvard
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Title: Connectomics analysis of hypothalamic parenting microcircuit using machine learning

Authors: *M. NG[1], X. M. HAN[2], R. SCHALEK[3], B. L. LOGEMAN[2], Y. WU[3], S. FINKBEINER[5], P. M. HORVATH[6], D. R. BERGER[4], D. WEI[7], J. W. LICHTMAN[3], C. G. DULAC[2];
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Abstract: Parenting behavior in mice is regulated by Gal+/Calcr+ neurons in the hypothalamic preoptic area (POA$^{Gal+/Calcr+}$ neurons), yet the organization and diversity of their synaptic inputs remain poorly understood. To address this, we developed a machine-learning-based pipeline to analyze and classify synaptic inputs onto POA$^{Gal+/Calcr+}$ neurons. Using volume-electron-microscopy-based connectomics data, we reconstructed incoming synaptic boutons onto POA$^{Gal+/Calcr+}$ neurons in a virgin female mouse. We applied SegCLR, a self-supervised representation-learning model, to compute 128-dimensional embeddings capturing bouton-level 3D morphology. In parallel, we applied VesiclePy to segment both small clear-core and large dense-core vesicles, enabling detailed characterization of synaptic ultrastructure. These complementary features capture distinct aspects of synaptic input identity. Because bouton morphology and synaptic vesicle composition correlate with neurotransmitter class, integrating these features generates higher-dimensional embeddings that cluster synaptic boutons into structurally and functionally distinct groups. Biologically grounded neurotransmitter class labels through dAPEX2-based genetic labeling enable validation of these embeddings. This work provides a scalable approach for quantifying synaptic diversity and developing a preliminary classifier to predict synaptic boutons' neurotransmitter class in connectomics data, ultimately enabling comparative analyses of hypothalamic parenting microcircuit across reproductive states.

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Nanosymposium

NANO31: Connectomics

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Time: Tuesday, November 17, 2026, 8:00 AM - 10:15 AM

Presentation Number: NANO31.07

Topic: J.03. Anatomical Methods

Support: Simons Foundation

Title: Connectome of the brain of a miniature wasp, Megaphragma viggianii

Authors: *K. SHINOMIYA[1], E. W. SCHOMBURG[1], J. WU[1], P. GUNN[1], S. BERG[2], M. ZLATIC[3], A. CARDONA[3], K. NAGEL[4], S. KIM[5], H. HESS[2], M. WERNET[6], A. POLILOV[7], D. B. CHKLOVSKII[1];
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Abstract: The miniature parasitoid wasp *Megaphragma viggianii* possesses one of the smallest brains among free-flying insects, yet retains a rich behavioral repertoire. This extreme miniaturization raises fundamental questions about how essential neural circuits are preserved under severe physical and cellular constraints. To address this question, we reconstructed a synaptic-resolution whole-brain connectome of an adult female *Megaphragma* using Focused Ion Beam Scanning Electron Microscopy (FIB-SEM). The resulting network comprises approximately 9,400 brain neurons, most of which are anucleate. These anucleate neurons exhibit a striking enrichment of putative RNA granules, frequently localized near presynaptic terminals, suggesting a mechanism for sustaining local protein synthesis and neuronal function despite the absence of nuclear transcription. Our connectome reveals that although extreme miniaturization drives circuit simplification and uneven reductions in neuron populations across cell types, the core architectures underlying visual processing, olfactory integration, and navigation remain conserved. *Megaphragma* implements these canonical circuit motifs with substantially fewer neuron types and greatly reduced cellular redundancy than *Drosophila*. In the visual system, the canonical ON and OFF motion pathways are retained, but are implemented with fewer neuron types and a simplified relay architecture. In the central complex, core columnar neurons preserve spatial topography, while context-providing tangential neurons are disproportionately reduced. Together, these findings show that *Megaphragma* preserves essential computational motifs while eliminating much of the redundancy present in larger insect brains, establishing this miniature wasp as a powerful model for comparative connectomics and whole-brain computational studies.

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Nanosymposium

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Support: CIHR DV2197706
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Title: TRACR: an anterograde transneuronal tracing system allowing genetic access across synapses and longitudinal circuit analysis.

Authors: M. IBRAHIMI[1,3], M. GRAY[4,5], S. EIRAS[5,3], P.-L. ROCHON[6], K. A. MARTEMYANOV[7], M.-E. PAQUET[8], A. KRISHNASWAMY[6], V. A. WALLACE[2], ***J. L. LEFEBVRE**[5,3];
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Abstract: Following neural signals as they converge onto and diverge from individual neurons is central to understanding circuit function and disease-related dysfunction. However, existing approaches for anterograde circuit tracing are limited by cytotoxicity, incomplete genetic control over connected partners, and permanent labeling that restricts analysis of connectivity changes during development or disease. To address these limitations, we developed TRACR—*TRanssynaptic Anterograde Circuit Readout*—a synthetic Notch-based tool for reversible transneuronal tracing. TRACR consists of two synthetic transmembrane components: a GFP ligand targeted to presynaptic terminals and a synthetic Notch receptor containing an anti-GFP nanobody and the heterologous transcription factor tetracycline transactivator (tTA). Binding between the engineered ligand and receptor induces Notch-like cleavage, releasing tTA to drive expression of a TRE-controlled reporter gene of choice in postsynaptic neurons. The TRACR design provides independent genetic access to pre- and postsynaptic populations and can be combined with markers, sensors, or effectors to characterize postsynaptic targets and expand circuit analysis. Using the mouse visual system, we show that TRACR can be restricted to genetically defined starter cells and used to efficiently and specifically label postsynaptic partners across sensory, local, and long-range circuits. Anatomical, molecular, and

electrophysiological analyses confirmed that TRACR reporter-positive neurons correspond to known postsynaptic partners. TRACR activation is synapse-dependent, as reporter expression is lost in mouse models in which photoreceptor synapses onto second-order neurons fail to develop or subsequently degenerate. Moreover, TRACR signals in target cells diminish following presynaptic degeneration and are reinstated upon synaptic reassembly, demonstrating reversibility and utility for monitoring connectivity changes over time. We have developed TRACR as a modular, AAV-deliverable toolkit for anterograde transneuronal tracing and longitudinal analysis of neural circuit assembly, organization, and degeneration.

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JP18dm0307006
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Title: Primate Common Coordinate Framework (CCF) and Extended Human Connectome Project (HCP) Pipelines for Multi-omics Neuroanatomy

Authors: *T. IKEDA[1], B. Q. ROSEN[2], T. COALSON[2], T. OSE[1], A. UEMATSU[1], N. YOSHIDA[1], T. ASO[1], J. A. AUTIO[1,2], K. NAKAMURA[4], Y. HOU[5], J. VEZOLI[5], D. HU[6], E. K. REID[2], A. A. BHANDIWAD[7], S. SOTIROPOULOS[8], F. LANGE[9], S. SMITH[9], W. FREIWALD[10], E. LEIN[7], H. KENNEDY[5,11], D. C. VAN ESSEN[3], M. F. GLASSER[2], T. HAYASHI[1,12,13];
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[11]Univ. Lyon, Bron, France; [12]Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [13]Natl. Inst. of Physiological Sci., Okazaki, Japan

Abstract: Non-human primate (NHP) neuroimaging lacks standardized resources and pipelines comparable to those provided by the Human Connectome Project (HCP) for humans, limiting cross-species comparisons and translational research. To address this gap, we introduce the Primate Common Coordinate Framework (Primate CCF), a unified platform designed to systematically integrate anatomical, functional, and molecular data across primate species. High-resolution T1-weighted, T2-weighted, functional MRI, and diffusion MRI data were acquired from rhesus macaques (*Macaca mulatta*, n=25), cynomolgus macaques (*Macaca fascicularis*, n=25), and common marmosets (*Callithrix jacchus*, n=25) on a 3T scanner equipped with multi-channel phased-array NHP coils. NHP-specific preprocessing functions were integrated into the HCP pipelines, incorporating volume reorientation, brain extraction, static magnetic field (B_0) distortion correction, and T2w-to-T1w registration using FreeSurfer boundary-based registration, with each step optimized for individual species. Cortical segmentation and surface reconstruction were performed using the FreeSurferPipelineNHP and FreeSurfer v6.0, while volume- and surface-based registration were executed by FSL FNIRT and multimodal surface matching (MSM), respectively. Templates were generated through group-wise averaging and dedrifting. These procedures yielded LR-symmetric, high-resolution templates for three NHP species: Mac25Rhesus, Mac25Cyno (0.5 mm isotropic), and MarmosetRIKEN25 (0.25 mm isotropic), alongside refined human reference data (HCP1071). The automated processing pipeline operates stably across all species, followed by quality control and manual surface editing. All surface metrics were mapped into CIFTI grayordinate spaces, ensuring compatibility with existing HCP visualization tools. The resulting MRI-based volume and surface templates accommodate legacy ex-vivo parcellations (NMT, D99, M150 for macaques, and SAM, Nencki-Monash, BMA for marmosets) mapped to spatial and surface coordinates. Furthermore, the platform features hierarchical visualization tools for multi-scale anatomical exploration and Atlas Ontology Model (AtOM) for FAIR-compliant metadata. Together, these components establish the Primate CCF as a robust, standardized framework for multi-species neuroimaging. This open-source platform and multi-species processing pipeline will bridge the gap between human and NHP connectomics and provide multi-omics infrastructure to accelerate comparative and translational neuroscience research.

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Nanosymposium

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Presentation Number: NANO32.01

Topic: B.08. Epilepsy

Support: Rowan University Camden Health Initiative

Title: Whole exome sequencing of a small nuclear family identifies novel risk alleles for familial focal epilepsy with variable foci (FFEVF

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Abstract: Rationale: FFEVF is a rare inherited epilepsy syndrome linked previously to causal variations in *DEPDC5, NPRL2* and *NPRL3* in ~10% of patients. We aimed to identify genetic variations linked to suspected FFEVF in three affected members of a small nuclear family. **Methods**: We consented eight family members and drew blood for DNA isolation and whole exome sequencing (WES). WES data were analyzed using DRAGEN germline and joint genotyping and the Integrative Genomics Viewer to align sequences and identify variants. We searched for *de novo* variations and tested variants using autosomal dominant (AD) and autosomal recessive (AR) inheritance models with incomplete penetrance based on the family pedigree. We queried all genes identified to determine their potential relationship to epilepsy phenotypes using GeneCards and the China Epilepsy Gene 1.0 Project database. We used Gene Ontology, DAVID and FUMA to examine if genes with variations that fit our models align in specific pathways and to analyze their expression patterns in normal tissues. Variants in genes were annotated using dbSNP and ClinVar. **Results**: We found no evidence for causative variations in *DEPDEC5, NPRL2* or *NPRL3*. We identified one *de novo* variation in an unaffected parent in *COL24A1* that is shared by all affected individuals and not present in any other database. A non-affected discordant monozygotic twin also inherited this mutation suggesting incomplete penetrance. We found 390 variations in 272 genes that fit the AD mode of inheritance,16 are related to epilepsy: *AKT3, DNM1, MTR, PDE2A, PIP5K1C, RALGAPA1, RYR2, SIRT3, SPTAN1, ST3GAL4, STT3A, STXBP1, TRAPPC6B, TRNT1, UBA6-DT, and ZFYVE26159*. We found 159 variations in 71 genes that fit the AR mode of inheritance, 8 related to epilepsy: *USH2A, SUCLA2, MGAT2, NID2, C3, UCHL1, GABRB1*, and *LNX*. None of the variations are pathological as defined by ClinVar or dbSNP. The 272 AD and 71 AR gene sets were analyzed by gene enrichment and pathway analyses, but no biological function or process was found to be significantly enriched. **Conclusion**: Results of this study support the conclusion that a rare de novo variation in the *COL24A1* gene is the cause of FFEVF in this family. Variants in *COL4A1* and *COL4A2* lead to neurological phenotypes that include epilepsy. Variants in *COL5A* and other collagen genes cause Ehlers-Danlos syndrome (EDS) and ~10% or more of EDS patients experience seizures. Lack of significant pathway enrichment in the AD and AR analysis also supports a monogenic cause. However, given that we found genes related to epilepsies in both the AD and AR analyses, it remains possible that the cause of FFEVF in this family is polygenic and involves combinations of alleles.

Disclosures: R.J. Buono: None. **R. Crist:** None. **T.N. Ferraro:** None. **H. Hakonarson:** None.

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Time: Tuesday, November 17, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO32.02

Topic: B.08. Epilepsy

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Title: Time-resolved spectral and functional network dynamics around interictal epileptiform discharges inform negative sample selection for automated detection models

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Abstract: Interictal epileptiform discharges (IEDs) are identified as paroxysmal events, however their effects on the surrounding visually normal EEG background remains poorly defined. Whether these peri-IED changes influence the selection of negative samples for automated IED detection is unknown. This study aimed to characterize spectral and functional-connectivity dynamics in visually non-IED EEG epochs near IEDs, and to evaluate their implications for negative samples selection for detection models. We analyzed 366 hours continuous scalp EEG recordings from 57 patients, containing 2,268 annotated IEDs. A total of 172,642 visually non-IED 4-second epochs were selected, and grouped according to their temporal distance from the nearest IED, separately for pre- and post-IED directions. For each epoch and frequency band, relative power spectral density (rPSD) was computed across electrodes, and functional connectivity was quantified using band-limited weighted phase-lag index (wPLI). rPSD differed significantly across distance after FDR correction. Delta and theta rPSD increased near IEDs, whereas beta and gamma rPSD decreased. Post-IED recovery time constants were 27.1s for delta, 29.3s for theta, 34.8s for alpha, 40.1s for beta, and 30.8s for gamma. Pre-IED onset time constants were 26.6s for delta, 21.7s for theta, 107.2s for beta, and 33.9s for gamma. Negative epochs within 30s of IEDs also showed significant wPLI differences, including higher theta, alpha, and beta, and lower gamma, all surviving FDR correction. To test whether this peri-IED state has functional consequences, we trained an EfficientNetV2 IED detector using 60,000 positive and 200,000 negative 4-second epochs. Validations on a fixed external test set showed that adding all 15,309 near-IED negatives (<30s) and supplementing to 30,000 epochs impaired to the baseline model, reducing AUPRC from 0.726 to 0.607, and precision at 80% recall from 49.4% to 35.4%. In contrast, adding intermediate-distance negatives (30-90s), normal negative samples, and negative samples remote from IED (>300s), all achieved increased AUPRC (0.759, 0.760, 0.764, respectively). These findings show that temporal distance from IEDs reveals physiologically meaningful heterogeneity within visually non-IED EEG. Quantitative rPSD and wPLI analyses support a peri-IED spectral-connectivity state that is invisible to routine visual labeling but relevant to both EEG interpretation and downstream computational modeling. Negative samples close to IEDs may therefore represent a perturbed peri-IED state, while more remote epochs may provide higher-quality negative samples for automated IED detection.

Disclosures: N. Lin: None. **Q. Lu:** None. **W. Gao:** None. **Y. dong:** None.

Nanosymposium

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Topic: B.08. Epilepsy

Support: Flinn Foundation

Title: Detection of Human Thalamocortical Network Communication utilizing Subcutaneous EEG Sensors

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Abstract: Deep Brain stimulation of thalamic nuclei is an effective therapy for treating patients with drug resistant epilepsy (DRE), but its therapeutic mechanisms in reducing seizure occurrence are still not understood. Thus, programming for patients is a time-consuming trial and error process. Previous work has shown that short-term DBS modifies thalamocortical communication. We demonstrate thalamic stimulation evoked potentials (EPs) measuring that communication is detectable by less invasive electrodes placed under the human subgaleal (SG) layer, enabling prospective studies on autonomous exploration of patient-specific stimulation parameter optimization. Eleven adults with DRE undergoing intracranial (IC) monitoring received single-pulse stimulation under an IRB protocol. Bilateral SG electrodes were implanted parasagittally. EPs to thalamic (anterior nucleus of the thalamus [ANT, N=9], or Pulvinar [PUL, N=7]) stimulation were recorded using 100 pulses (4mA amplitude, 3-7s interstimulus interval). In a subset of patients (ANT target, N=4), network modification was assessed using 300 single pulses at 2Hz both before and after 18 minutes of continuous 145Hz stimulation at 3mA. Responses were quantified utilizing amplitude (zPeak), energy (RMS), waveform complexity (line length), and trial-to-trial consistency (PC) in the stimulation window (15-200ms) to a baseline window (-200--15ms). Spatial effects were evaluated using mixed-effects models and network modification was tested with pointwise two-sample t-tests comparing pre- and post-stimulation EPs. SG recordings detected cortical EPs that preserved IC response morphology. Mixed-effects modelling confirmed a spatial bias. The strongest effect was ipsilateral predominance over contralateral recording: zPeak, $\beta=5.24$, $p<0.0001$; RMS, $\beta=2.42$, $p<0.0001$; PC, $\beta=0.0590$, $p<0.0001$. More anterior contacts also showed stronger responses than posterior contacts: zPeak, $\beta=0.734$, $p<0.0001$; RMS, $\beta=0.399$, $p<0.0001$; line length, $\beta=0.0725$, $p<0.0001$; PC, $\beta=0.0166$, $p=0.003$. Together, these findings identify a consistent spatial optimization principle: ANT-EPs are strongest on the anterior ipsilateral SG electrode, concentrated near the coronal suture. This spatial distribution of EPs differed across thalamic nuclei stimulated. PUL showed a more posterior ipsilateral distribution, consistent with their differing structural connectivity. SG thalamic EP modifications were detectable in all evaluable patients (N=4). In

each case, pre- vs post-stimulation EPs differed significantly ($p<0.01$), with deviations concentrated approximately 30-65ms after the pulse.

Disclosures: T.D. Johnson: None. **B. Mohan:** None. **B. Layton:** None. **J.J. Parker:** None.

Nanosymposium

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Title: Antiseizure Medications Induce Drug-Specific Shifts in the Aperiodic Exponent of Chronic Ambulatory Intracranial Electrocorticography

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Abstract: The aperiodic exponent (1/f slope) is a putative biomarker for treatment response of CNS-active medications, thought to reflect the excitation-inhibition (E/I) ratio, with a steeper exponent reflecting greater inhibition. Antiseizure medications (ASMs) modulate E/I in the brain through diverse mechanisms, yet whether they shift the aperiodic exponent in humans, and if such shift is mechanism-specific, remains unclear. We analyzed 26,288 ‘scheduled’ electrocorticograms (ECoGs) from brain-implanted responsive neurostimulation (RNS) devices in 27 adults with medically refractory epilepsy (mean age 41 years, 51.9% female) who started new ASMs. After removing artifacts (electrical stimulations, interictal epileptiform activity, seizures) we fit the aperiodic exponent to the remaining background activity by spectral parameterization in the frequency range [1,75] Hz (mode “knee”). Pre- and post-medication periods (±60 days) were compared for 7 newly initiated ASMs (cenobamate, brivaracetam, clobazam, cannabidiol, clonazepam, gabapentin, and levetiracetam). A linear mixed model (LMM) regressed the exponent against medication status, ASM interaction, time trends, and diurnal variations. Random effects controlled for patient-specific baselines and channels. Sensitivity analyses evaluated the fit across 8 frequency ranges. The pre-to-post shift in aperiodic exponent differed across ASMs (medication-status × drug interaction, $\chi^2(6) = 313$, $p < 0.0001$). A shared upward drift followed initiation across all drugs (+0.0013/day, $p < 0.0001$; ~ +0.08 over 60 days), consistent with accruing inhibition. Cenobamate ($n = 16$) initiation was associated with the most prominent 1/f steepening (+0.13, $p = 0.02$). Conversely, clonazepam (-0.26, $p < 0.0001$) and brivaracetam (-0.16, $p = 0.005$) were associated with relative flattening of the slope, and the remaining four medications' exponents did not shift significantly. The aperiodic exponent was robust to the low-frequency bound ($r \geq 0.95$ vs the [1-75] Hz primary across [2-75], [3-75], [4-75] Hz); it was more sensitive to the upper bound to 40-45 Hz, consistent with the knee model's dependence on the high-frequency tail. ASM initiation shifted the aperiodic exponent

overall and in a drug-specific manner, most prominently for cenobamate. The aperiodic exponent may serve as a within-individual indicator of ASM-induced E/I perturbation. Limitations include small per-drug samples (N = 5-16), co-titration, dose heterogeneity, and observational design.

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Title: Brain States Associated with Termination of Native and Cognitively Interrupted Induced Seizures in Drug-Resistant Epilepsy

Authors: *M. KHOSHKHOU[1], R. P. LESSER[2], S. V. SARMA[3], J. KANG[4];
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Abstract: Understanding how neural networks naturally recover from seizure activity and return to normal function remains a fundamental unanswered question in epilepsy research. Elucidating these mechanisms could uncover the network dynamics governing transitions from pathological to normal brain states and enable novel therapeutic targets for neuromodulation therapies aimed at improving outcomes for the more than 17 million people worldwide living with drug-resistant epilepsy (DRE). To identify the network mechanisms underlying seizure termination, we analyzed intracranial EEG (iEEG) recordings from 7 patients with DRE during both native seizures and induced seizures in which brief cognitive interventions were applied to suppress seizure activity. We hypothesized that termination of spontaneous seizures and cognitively interrupted induced seizures engage similar brain networks that rapidly drive the epileptic network toward native non-ictal states. To test this hypothesis, we estimated a dynamical network model from iEEG recordings, computed source-sink indices to characterize network influence patterns, and revealed recurrent brain states using k-means clustering. Each recurrent brain state corresponded to a distinct network configuration of the epileptic brain. We found that interictal, ictal, and postictal periods were characterized by distinct dominant brain states. Although brain states were patient-specific, they exhibited common features across patients. In every patient, we observed a recurrent termination-associated brain state that was consistently engaged during both spontaneous termination of native seizures and termination of cognitively interrupted induced seizures. The termination state is marked by dominant source nodes exerting strong influence on the seizure onset zone. Successful cognitive interventions engaged this state,

supporting the notion that both seizure types converge on common mechanisms that drive the epileptic brain toward native non-ictal states. Compared with induced seizures, native seizures exhibited more complex trajectories through state space before reaching the termination state. Brain regions exerting strong influence within this state may represent promising targets for neuromodulation therapies designed to engage endogenous mechanisms that restore normal brain function.

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Nanosymposium

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Title: Focal Cooling Disrupts Seizures in a Non-Human Primate Model of Epilepsy

Authors: *E. ADESSO[1,2], C. S. SIMÕES[4], T. COSTECALDE[5], N. AUBERT[6], J. MOLET[3], S. CHABARDÈS[7], N. TORRES[8], J. FABER[9];
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Abstract: The electroencephalogram (EEG) remains the gold standard for epilepsy diagnosis, classification, and monitoring. However, EEG interpretation remains challenging due to the intrinsically nonlinear and nonstationary nature of neurophysiological signals. This complexity is particularly relevant when assessing seizure-suppression strategies such as focal cooling of epileptogenic zones. Previous studies have shown that focal cooling can reduce seizure frequency and duration, and in some cases completely suppress seizures. To investigate how cooling modulates residual epileptiform activity at different temperatures (25 °C, 23 °C, 21 °C, and 17 °C), we applied two complementary computational approaches to characterize epileptic network dynamics. The first approach consisted of Recurrence Quantification Analysis (RQA), while the second involved Kullback-Leibler (KL) divergence applied to empirical probability

distributions derived from amplitude, spectral, phase, and recurrence-based signal features. These analyses were performed on stereotactic hippocampal EEG (sEEG) recordings obtained from two non-human primate (NHP) models of temporal lobe epilepsy. Baseline activity was compared with seizures recorded both with and without focal cooling. KL-based analyses revealed that seizures cooled at 21 °C differed markedly from all other cooled and untreated seizures, exhibiting significantly higher values for most RQA-derived coefficients. In contrast, seizures cooled at 25 °C showed partial similarity to untreated seizures. Among the different feature-based approaches combined with KL divergence, recurrence-based features provided the best discrimination between baseline, untreated and cooled seizures using canonical discriminant analysis (CDA). RQA results suggest that focal cooling does not suppress seizure activity by eliminating determinism or inducing randomness, but rather through a reorganization of pathological dynamics. In particular, the 21 °C condition may represent a dynamical critical point at which local synchronization coexists with global disruption of seizure propagation. KL divergence analyses further suggest a partial suppression of the epileptic network while preserving smaller synchronized subnetworks. These residual subnetworks may generate signals enriched in recurrence structures, potentially explaining the high sensitivity of recurrence-based analyses to cooling-induced dynamical changes. Overall, this work highlights the potential of KL divergence and RQA as sensitive tools for neurophysiological signal analysis providing further insight into the dynamics of epileptic networks.

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Nanosymposium

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Presentation Number: NANO32.07

Topic: B.08. Epilepsy

Title: Automated Quantitative Phenotyping of Seizure Semiology Using 3D Poses Reconstructed from Routine Epilepsy Monitoring Unit Single-camera Videos

Authors: *Y. SHI, S. AGASHE, T. W. DUNN;
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Abstract: Seizure semiology provides important information for clinical epilepsy evaluation, yet characterization of seizure motor manifestations remains largely qualitative and dependent on expert review. While recent machine learning approaches have shown promise for end-to-end seizure detection and seizure classification from video recordings, comparatively little work has focused on automated extraction and quantitative characterization of clinically meaningful semiologic signs. Leveraging recent advances in machine learning and computer vision, we developed an automated pipeline for single-camera 3D pose reconstruction and quantitative phenotyping of seizure semiology from epilepsy monitoring unit (EMU) videos. The framework

combines a customized 2D pose estimation model, adapted to be robust within the busy EMU environment, with post hoc 3D pose reconstruction to enable analysis under challenging clinical conditions, including scenes containing caregivers, medical staff, and partial body occlusion from bedding and blankets. Quantitative behavioral trajectories captured multiple seizure motor manifestations, including unilateral head version, figure-of-4 posturing, clonic activity, and bilateral tonic extension. Automated extraction of clinically relevant lateralizing signs demonstrated perfect agreement with expert annotations, achieving 100% accuracy for head turn direction and figure-of-4 laterality, though automatisms and lip twitching are hard to detect on the current whole-body detection pipeline due to a lack of corresponding keypoints. Beyond categorical semiologic labels, the framework quantified continuous kinematic features including head rotation angle, keypoint angular velocity, clonic frequency, and clonic amplitude. Repeated seizures exhibited similar kinematic trajectories within individual patients, suggesting that quantitative motor phenotypes may capture reproducible patient-specific seizure signatures. Preliminary analyses revealed variability in these measurements across seizures sharing the same semiologic annotations, providing a basis for future investigation of motor features that are difficult to characterize systematically using conventional semiologic annotations alone. Application of the framework to larger cohorts may enable identification of motor phenotypes associated with seizure subtypes, epileptogenic zones, and patterns of seizure propagation.

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Nanosymposium

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Title: Human and experimental temporal lobe epilepsy is characterized by aberrant m6A patterning

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Med. and Hlth. Sci., Dublin 2, Ireland; [4]Dept. of Physiol. and Med. Physics, Royal Col. of Surgeons in Ireland, Dublin, Ireland; [5]Royal Col. Surgeons Ireland, Dublin, Ireland

Abstract: N6-methyladenosine or m6A, the most abundant internal modification of RNA, regulates RNA fate in several ways including stability and translational efficacy. To understand the yet unknown role of m6A, hippocampal samples from mice that received intra-amygdala kainic acid injections or human patients with drug refractory TLE were used to perform the first comprehensive m6A profiling in epilepsy. Disruption of m6A regulating enzymes were observed both during epileptogenesis and in chronic epilepsy in mice, while similar disruptions were evident in human TLE. Specifically, we detected elevated levels of METTL3 in both models, suggesting enhanced m6A deposition as a feature of the hyperexcitable brain. To characterise the transcriptome-wide m6A profile in epilepsy, we performed an m6A array, again in tissue from both epileptic mice and humans. This demonstrated that the epileptic brain is characterised by hypermethylation. This hypermethylation phenotype was established early following an epileptogenic insult and persisted throughout disease and hypermethylated transcripts were associated with cell viability, synaptic plasticity, metabolism and inflammation. Parallel proteomic profiling of human TLE tissue identified a negative correlation between m6A status and protein abundance suggesting m6A, in the context of epilepsy, promotes degradation of mRNA transcripts or inhibits their translation. To assess the functional implications of hypermethylation in epilepsy we are now exploring the effect of m6A modulation on seizure outcomes in mice.In summary, we identify aberrant RNA methylation as a novel contribution to the gene dysregulation that promotes epilepsy development. This pathway may represent a novel therapeutic target for the treatment of epilepsy.

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Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

Location: WCC Rm 140

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Title: Representation of infant cues driving pup avoidance in the mouse central amygdala

Authors: *C. A. MENGDEN[1], C. J. BAIR MARSHALL[2], A. AGHA[3], M. SELLES[4], M. BKHIET[6], R. C. FROEMKE[5];

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Abstract: Infants in distress use a variety of cues to communicate their needs to potential caregivers. In parents and experienced alloparents, infant distress cues induce approach and care, but the same cues are often aversive to non-caregivers, leading to neglect, avoidance, or maltreatment (Isogai et al., 2018, *Cell*; Mei et al., 2023, *Nature*). While the systems promoting infant-directed care have been well explored, how the brain processes infant cues to drive avoidance and aversion is less understood. Understanding the neural basis of infant avoidance is important to understanding the plasticity underlying the transition to caregiving (Dulac et al., 2014, *Science*; Marlin et al., 2015, *Nature*; Froemke & Young, 2021, *Annu. Rev. Neurosci.*), as well as providing insights to the neural basis of disorders related to aversion to social sensory cues. We investigated the neural circuits activated by first contact with pups in nulliparous (virgin) female C57Bl/6 mice and the changes in these circuits following co-housing experience with a lactating dam and her litter. Whole-brain cFos profiling showed that there was strong activity in the central nucleus of the amygdala (CeA) when mice were first exposed to infants (N=4 pup exposed, N=4 non pup exposed). We performed fiber photometry to monitor bulk Ca^{2+} activity in CeA cells that project to the locus coeruleus (LC; CeA-LC projectors). CeA-LC projectors had a robust response to pups in naïve virgin females, but not in experienced allomothers (N=6, p=0.003). We found that CeA-LC projectors responded to the individual sensory components of an infant by testing responses to a dummy pup (visual), pup calls (auditory), and pup-scented bedding (chemosensory; N=6 animals, all $p<0.05$). We then tested the functional role of CeA-LC activity and found that we could control infant-directed approach and avoidance by optogenetically manipulating CeA-LC terminals in the LC. In experienced allomothers, excitation of CeA-LC terminals decreased interaction with infants (N=8, p=0.0068). These data collectively point to a role for the CeA and its projection to the LC in regulating avoidance and approach to social stimuli, opening a potential role for the CeA in social sensory processing and emotional regulation.

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Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

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Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.02

Topic: E.08. Multisensory Integration

Support: Misophonia Research Fund

Title: Investigating Excitatory/Inhibitory Neurochemical Balance in Misophonia and Loudness Hyperacusis

Authors: *H. MEHMOOD[1], P. B. CAMACHO[3], F. LAM[2], X. LI[2], F. T. HUSAIN[1];
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Abstract: Sound intolerance disorders can significantly impair daily functioning, disrupt social interactions, and cause emotional distress. However, their neurobiological mechanisms remain poorly understood. Misophonia is a condition that triggers strong emotional reactions to specific sounds, while hyperacusis is characterized by physical discomfort or pain from ordinary sounds. Prior work on tinnitus suggests that altered balance between excitatory (glutamate/glutamine; Glx) and inhibitory (Gamma-aminobutyric acid; GABA) neurotransmission may contribute to abnormal auditory perception; however, a previous study on misophonia did not find any significant effects. This study uses a high-resolution, targeted magnetic resonance spectroscopy (MRS) protocol to examine whether misophonia and loudness hyperacusis are associated with altered E/I ratios within the central auditory pathway, targeting subcortical nuclei including the cochlear nuclei, superior olivary complex, and inferior colliculus, and the primary auditory cortex. The rectangular field of view was angled at approximately 45° and aligned through the inferior colliculus to improve spatial resolution in these regions. Participants (N = 92; ages18-25 years; 32 male, 60 female) were drawn from a survey and categorized into misophonia (MIS), hyperacusis (HYP), comorbid (MH), or control (CTR) groups. The resulting concentration maps allowed us to compute ratios such as GABA/Cre, Glx/Cre, and Glx/GABA and compare these across MIS, HYP, MH, and CTR groups. Preliminary analyses investigated each neurochemical signature across these phenotypes. Within targeted subcortical structures, the HYP group exhibited the lowest median GABA/creatine (Cre) levels and the highest Glx/GABA ratios, indicating a shift toward central excitation, while MIS participants displayed a slightly higher Glx/GABA ratio than controls; the MH group did not differ from the controls. By clarifying the neurochemical basis of these disorders, this project could contribute to improved diagnostic approaches and inform future intervention strategies. More broadly, this work could lead to establishing neurochemical biomarkers by linking specific neurotransmitter profiles to sound intolerance phenotypes.

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Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.03

Topic: E.08. Multisensory Integration

Support: Misophonia Research Fund

Title: Comparing Misophonia with Clinical Emotional Dysregulation: A Multi-method Characterization Study

Authors: *Z. E. BRASHER, J. Y. CHOI, S. C. NAPOLITANO, L. D. KELLEY, A. D. NEACSIU;
Psychiatry and Behavioral Sci., Duke Univ., Durham, NC

Abstract: In misophonia, specific everyday sounds evoke intense distress and reactivity. Although associated with emotion dysregulation and impairment, few studies have directly compared misophonia to other clinical groups, limiting mechanistic understanding and intervention development. To address this gap, we conducted a multimethod study comparing adults with moderate-severe misophonia and adults with clinically significant emotion dysregulation.
Adults with elevated misophonia symptoms (n = 30) or clinically significant emotion dysregulation without misophonia (n = 29) were enrolled. All completed a structured clinical interview to confirm DSM-5 diagnoses and self-report measures assessing misophonia (MQ), emotion dysregulation (DERS), efficacy in emotion regulation (ERQ) confidence with managing negative emotions (PROMIS-SEME), impairment (WSAS). Group differences in physiological indices of sympathetic and parasympathetic function were examined across an experimental protocol at baseline, during an evocative sound task, and post-task using skin conductance level (SCL) and high-frequency heart rate variability (HF-HRV) in general linear models for each period.
Participants with misophonia reported lower generalized emotion dysregulation ($P<0.001$), greater confidence managing negative emotions($p=0.001$) than the emotion dysregulation group despite similar impairment ($ps>0.05$). After Bonferoni correction, there was insufficient evidence of differences in self-reported overall regulatory ability or sensitivity to emotion ($ps>0.05$). At baseline, physiologically, participants with misophonia exhibited higher HF-HRV ($t(56)=2.39$, $p=.020$) and more frequent SCRs ($t(56)=2.07$, $p=.043$), than clinical controls, and no evidence of a difference in SCL ($p=.244$). During sound task, groups significantly differed in HF-HRV, ($F(1,54)=6.08$, $p=.017$, $\eta p^2=.10$), such that the misophonic group exhibited higher HF-HRV; this effect persisted through post-task ($F(1,54)= 5.18$, $p=.027$, $\eta p^2=.09$), above and beyond the effect of baseline HF-HRV ($p<.001$). No group differences were observed in task or post-task SCL or SCR after adjustment for baseline values ($ps=.725-.856$).
Despite clinical impairment, individuals with misophonia displayed a distinct regulatory profile: elevated parasympathetic, but not sympathetic, activity persisted through the evocative task and post-task recovery, indicating sustained parasympathetic engagement compared to individuals without misophonia. Thus, misophonia appears to reflect stimulus-bound reactivity and recovery in those who otherwise regulate well.

Disclosures: Z.E. Brasher: None. **J.Y. Choi:** None. **S.C. Napolitano:** None. **L.D. Kelley:** None. **A.D. Neacsiu:** None.

Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.04

Topic: E.08. Multisensory Integration

Support: Misophonia Research Fund

Title: When Sounds Strike a Nerve: Severity-Linked Emotional Reactivity in Misophonia

Authors: *J. Y. CHOI, A. D. NEACSIU, S. C. NAPOLITANO;
Psychiatry and Behavioral Sci., Duke Univ., Durham, NC

Abstract: Background: Misophonia is a disorder of decreased sound tolerance, involving marked affective and bodily responses to everyday sounds. Prior studies have compared diagnostic groups using small experimenter-selected stimulus sets, leaving unclear whether reactivity varies continuously with misophonia severity or whether participant-perceived trigger status improves prediction. **Methods:** Fifty-six age- and gender-matched adults, including 28 participants with misophonia and 28 clinical controls with a DSM-5 disorder and high emotion dysregulation, completed a laboratory sound task with 89 researcher-classified misophonic, aversive, or neutral sounds. Skin conductance response frequency and galvanic skin response amplitude were recorded with ratings of emotional valence, emotional intensity, and categorical emotion labels. Participants with misophonia also indicated whether each sound was a personal trigger. Mixed-effects and Bayesian models tested whether misophonia severity moderated associations between sound category and emotional or physiological responding, and the concordance between researcher-defined and participant-defined sound classifications.**Results:** Greater misophonia severity was associated with stronger responses to misophonic sounds, including higher SCR frequency, Sound Type x Severity: $b = 0.029$, $SE = 0.009$, $p = .001$, and emotional intensity, $b = 0.06$, 95% CrI [0.04,0.08], $OR = 1.06$. For aversive sounds, the opposite pattern was observed for emotional intensity, $b = -0.05$, 95% CrI [-0.076, -0.03], $OR = 0.965$. Misophonic sounds were more likely to be labeled with anger and disgust, while aversive sounds were more likely to be labeled with fear and sadness, regardless of misophonia severity. GSR amplitude was not significantly moderated by severity across sound categories. Researcher-defined and participant-defined classifications showed substantial agreement, Cohen's $\kappa = 0.671$, $z = 8.95$, $p < .001$. Participant-classified misophonic triggers evoked stronger emotional than aversive sounds, $b = 3.05$, 95% CrI [2.46, 3.65], $OR = 21.12$, and were more likely to elicit anger and disgust.**Conclusion:** Findings suggest that misophonia-related sound reactivity varies with disorder severity and is most clearly reflected in subjective emotional experience. This pattern supports an appraisal-based account in which personally meaningful interpretations of sound shape the strength and quality of affective responses. In contrast, sympathetic arousal appeared less sensitive to severity-linked differences, highlighting future mechanistic and intervention targets.

Disclosures: J.Y. Choi: None. **A.D. Neacsiu:** None. **S.C. Napolitano:** None.

Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.05

Topic: E.08. Multisensory Integration

Support: R01 DC 004290

Title: Investigating neural responses to aversive sounds with human intracranial EEG

Authors: *L. M. KING[1], H. KAWASAKI[4], A. E. RHONE[2], N. T. TRAPP[3], K. R. BIJANKI[5], M. A. HOWARD, III[4], T. D. GRIFFITHS[6], S. KUMAR[2], J. I. BERGER[2];
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Abstract: Sounds can have prominent effects on mood and daily living, particularly those that people perceive as aversive. Prior research has identified that aversive sounds are associated with increased activation of the insula, amygdala, and auditory cortex (PMID: 40859135; PMID: 23055488; PMID: 31101901). However, extant literature has mainly used fMRI wherein the temporal resolution is limited, while the response to aversive sounds has not been previously studied using the high spatiotemporal resolution offered by intracranial electroencephalography (iEEG). Thus, the present study used iEEG to determine how aversive sounds influence frequency-specific neural responses in regions previously implicated in aversive stimulus processing, restricting analyses to the insula, auditory cortex, precentral gyrus (PreCG), postcentral gyrus (PostCG), and regions of the limbic system. iEEG was recorded from nine neurosurgical patients while they listened to aversive (e.g., alarm) and neutral (e.g., rain) sounds, categorized based on ratings from prior work and matched for sound level. Data were cleaned offline and time-frequency analyses were performed by convolving the data with Morlet wavelets. Recording sites were localized based on pre- and post-operative MRI anatomical reconstructions. Responses in anterolateral Heschl's gyrus (HGAL) were stronger for aversive stimuli than neutral auditory stimuli. Specifically, HGAL demonstrated higher power for aversive stimuli compared to neutral for low gamma ($p = .002$) and high gamma ($p = .013$) bands, concurrent with reduced power in delta ($p = .018$) and theta ($p = .008$) bands. Responses to aversive auditory stimuli in anterior insula were significantly increased in the beta band compared to neutral stimuli ($p < .001$). Significant differences in average power between aversive and neutral auditory stimuli were also observed in the PreCG and PostCG, the direction of which varied depending on the specific frequency band. No significant differences were observed in the amygdala, which is perhaps because many of the aversive sounds may have lacked high enough salience to impact amygdala activity or because the amygdala may have adapted to the stimuli more quickly than other regions. Nevertheless, this result is consistent with some previous literature in the visual domain (PMID: 25142122). These results suggest that the HGAL, anterior insula, PreCG, and PostCG play a crucial role in the processing of aversive auditory stimuli. Overall, these results highlight regions and frequency bands of interest that should be further explored in clinical populations with selective sound sensitivities, such as those with misophonia.

Disclosures: L.M. King: None. **H. Kawasaki:** None. **A.E. Rhone:** None. **N.T. Trapp:** None. **K.R. Bijanki:** None. **M.A. Howard:** None. **T.D. Griffiths:** None. **S. Kumar:** None. **J.I. Berger:** None.

Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.06

Topic: E.08. Multisensory Integration

Support: Misophonia Research Fund

Title: Reduction of Auditory N1 and P2 ERP Components During Misophonia, ASMR, and Musical Chills Videos

Authors: *I. MCCONLEY[1], D. VOLLWEILER[1], E. HANNON[1], J. SNYDER[2];
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Abstract: Auditory affective experiences like misophonia, the autonomous sensory meridian response (ASMR), and musical chills can induce a range of behavioral and physiological reactions, including increased activity in the salience network, suggesting that these experiences are attention-grabbing. We might therefore expect these experiences to influence attention-sensitive event-related potentials (ERPs). Additionally, less is known about the development of these experiences and their influence on attention across age groups. This study uses ERPs and self-report measures of emotion to explore neural signatures of misophonia, ASMR, and musical chills in adults and in cross-sectional child populations, and asks whether they reduce N1 and P2 ERPs to tones. During ERP recording, participants watched videos meant to induce misophonia, ASMR, or chills. They also participated in neutral video and no video control conditions. During each video, a series of tones played in the opposite ear from the video's audio track. Preliminary findings from 63 adult participants show reduced N1 and P2 components during misophonia videos compared to the other video conditions; in contrast, 26 child participants show N1 reductions for all video types compared to the tones-only condition, but greater P2 reduction for misophonia compared to other video conditions. These findings suggest that the N1 and P2 responses might be a useful measure of the attention-grabbing aspect of misophonia and for assessing misophonia treatment outcomes.

Disclosures: I. McConley: None. **D. Vollweiler:** None. **E. Hannon:** None. **J. Snyder:** None.

Nanosymposium

NANO33: Neuronal Mechanisms of Misophonia

Location: WCC Rm 140

Time: Tuesday, November 17, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO33.07

Topic: E.08. Multisensory Integration

Support: Misophonia Research Fund

Title: Impaired Reversal Learning in Misophonia: Behavioral and Neural Evidence from EEG

Authors: *P. JAIN[1], A. CHEN[2], A. A. THINAKARAN[3], A. PETERS[4], J. TRAYVICK[5], X. GU[6], J. H. FOSS-FEIG[1], D. SCHILLER[1];
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Abstract: Misophonia is characterized by heightened emotional responses to certain common sounds (e.g., chewing, sniffing, and coughing), especially in social contexts. While the mechanisms of misophonia are still elusive, dysfunctions in affective learning are a plausible mechanism. Here, we tested this hypothesis by examining the behavioral and neural mechanisms of affective learning in participants with misophonia compared to neurotypical participants.
To this end, we used a reversal-learning task to study associative learning and its adaptability. We associated neutral visual cues with neutral sounds or misophonia triggers and reversed the association through the task. Participants were asked to report how unpleasant they found the visual cues before the beginning of the task, before reversal, and at the end of the task. Higher negative ratings for the cue associated with misophonia triggers would indicate successful learning. EEG was recorded during the task and visual-cue related event-related potentials (ERP) and event-related spectral perturbation (ERSP) were analyzed. For the ERP, we measured the amplitudes and latency of P1, N1, and P2 peaks which denote pre-attention, cued attention, and perceptual processing and memory, respectively. For the ERSP, we measured the power and inter-trial coherence of different frequency bands during the first 500 ms after the presentation of the visual stimulus. The theta (4-8 Hz) and beta (12-30 Hz) bands are associated with learning and visual processing and were particularly of interest.
The behavior of both subject groups was identical during acquisition but differed after reversal. Neurotypical participants (n=38) rated only misophonia sounds as unpleasant, whereas participants with misophonia (n=29) rated both misophonia and neutral sounds as unpleasant at the end of the task. In other words, people with misophonia find the neutral cue unpleasant even after it is no longer associated with misophonia trigger. Additionally, we found differences in ERP and ERSP of the two groups in the parietal region. Misophonia participants had higher ERP amplitudes and higher ERSP power (specifically in the theta and beta bands) than neurotypical participants.
Our findings indicate that dysfunction in adaptive learning, manifested as an inability to update associations between neutral cues and misophonia triggers. Evidenced by ERP and ERSP, this behavior is accompanied by enhanced neural activity in the parietal region. These findings support maladaptive affective learning as a plausible mechanism involved in misophonia and suggest new avenues for its treatment approaches.

Disclosures: P. Jain: None. **A. Chen:** None. **A.A. Thinakaran:** None. **A. Peters:** None. **J. Trayvick:** None. **X. Gu:** None. **J.H. Foss-Feig:** None. **D. Schiller:** None.

Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.01

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Burroughs Wellcome Fund Career Award for Medical Scientists
ITMAT Pilot Grant

Title: Complementary Neuroimaging Approaches to Mapping Maternal Brain Plasticity

Authors: *S. SHANMUGAN;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Pregnancy is a time of profound neuroendocrine, physiological, and behavioral change. Yet how the human brain adapts across this transition remains incompletely understood. In this talk, I will present recent and unpublished work from two studies that use complementary approaches to map maternal brain plasticity.

First, the bulk of the presentation will focus on our work using a dataset of more than 5,000 clinically-acquired brain MRIs from women scanned prior to conception, during pregnancy, or in the postpartum. For this study, we use an AI-assisted pipeline (Fig 1A) that synthesizes and segments heterogeneous clinical brain images (Fig 1B), enabling their use for research. Results from an initial sample of 515 patients who have undergone image preprocessing and medical record curation demonstrate decreases in global and regional gray matter volumes during pregnancy that partially recover in the postpartum (Fig 1C-D). Additional symptom-linked analyses suggest lower gray matter volume among individuals with perinatal depressive symptoms (Fig 1E). This resource enables the study of maternal brain plasticity across a large, diverse sample of women.

In a second study, we complement this scale with an ongoing prospective, multimodal cohort designed to characterize person-specific maternal brain plasticity (Fig 1F). This work highlights methodological considerations for hemodynamic neuroimaging during pregnancy. Pilot, within-participant findings suggest that maternal position (eg supine vs left lateral tilt) during scanning may impact hemodynamic MRI metrics (Fig 1G).

Together, these studies illustrate complementary opportunities and challenges of using large-scale clinical imaging and deeply phenotyped prospective cohorts to map the maternal brain.

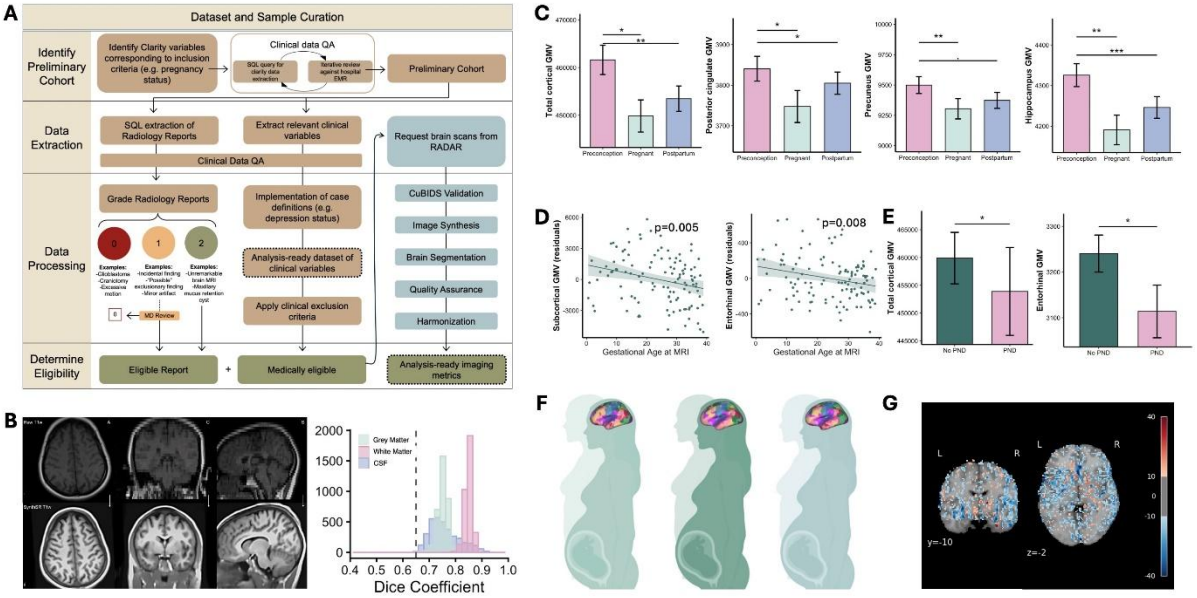


Fig. 1. Complementary approaches to mapping the maternal brain. A) Clinical dataset curation pipeline. **B)** Representative T1 before and after super-resolution synthesis with SynthSR (left). Distribution of Dice coefficients for SynthSeg-derived tissue segmentations, demonstrating reliable segmentation performance in 97% (n=3433) of scans (right). **C)** In an initial sample of 515 patients who have undergone image preprocessing and medical record curation, associations between pregnancy and GMVs were evaluated using linear models controlling for maternal age. GMVs were significantly lower during pregnancy compared to preconception. GMV increased in the postpartum but remained lower than preconception levels. **D)** GMV was significantly negatively associated with gestational age during pregnancy. **E)** Patients with perinatal depressive (PND) symptoms exhibited lower total cortical GMV as well as lower GMV in regions implicated in depressive symptoms. **F)** Complementing the scale of clinical imaging, prospective longitudinal cohorts allow for multi-modal imaging and deep phenotyping. **G)** Difference in cerebral blood flow between left lateral tilt and supine positions in a participant at 33 weeks gestation. *p<0.05, **p<0.01, ***p<0.001

Disclosures: S. Shanmugan: None.

Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.02

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Reprograms
Ann S. Bowers Women's Brain Health Initiative

Title: Dynamic changes in brain structure and cerebrovasculature across the perinatal transition

Authors: *H. GROTZINGER[1], E. G. JACOBS[2];
[1]Univ. of Virginia, Charlottesville, VA; [2]UC Santa Barbara, Santa Barbara, CA

Abstract: While 80% of women experience pregnancy at least once in their lifetime, there is virtually no knowledge of how the human brain changes across gestation. Recent advances in maternal brain research have shed light on the comprehensive structural changes that occur over the perinatal period: gray matter volume (GMV) and cortical thickness (CT) consistently decrease during pregnancy and increase in the postpartum. In addition, estradiol is a potent

vasodilator, and during pregnancy blood flow increases by ~30-50% and cardiac output increases by 50%. Yet, little is known of how cardiovascular adaptations during pregnancy impact cerebral blood flow (CBF).Here, we mapped structural and cerebrovascular adaptations to pregnancy across the gestational window. Six female participants planning a pregnancy (5 primiparous, 1 multiparous) and 5 nulliparous female controls completed MRI up to ~30 times from pre-conception through one year postpartum. At each session, participants completed a questionnaire to assess mood and sleep quality, an MRI scan consisting of whole-brain structural sequences and a pseudo-continuous arterial spin labeling sequence to directly map CBF across gestation, and a blood draw.Consistent with our lab's previous findings, Generalized Additive Models revealed significant relationships in all participants between GMV and gestation week ($p < 0.001$) and CT and gestation week ($p < 0.001$), with both structural measures showing linear decreases across gestation with a slight rebound in the postpartum period. Additionally, all participants displayed increases in CBF from baseline to a peak mid-gestation, followed by decreases until birth ($p < 0.001$).Control of blood flow to the brain is vital, and pregnancy is a transition period marked by increased susceptibility to cardiovascular conditions. Importantly, hypertensive disorders during pregnancy have been correlated with negative outcomes later in life in both cognitive function (Miller et al. 2024) and cerebrovascular integrity (Canjels et al., 2022). Understanding individual trajectories in cerebrovascular adaptations to healthy pregnancies may help evaluate the underlying pathology of these conditions. Taken together, these findings indicate that the brain undergoes a massive transformation during gestation, leading to changes in brain structure and CBF that are consistent in five densely-sampled participants. As data collection continues, this study is poised to provide the scientific community with the most detailed examination of the neurobiology of human pregnancy to date, offering new avenues for scientific discovery to drive advancements in women's brain health.

Disclosures: H. Grotzinger: None. **E.G. Jacobs:** None.

Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.03

Topic: G.02. Neuroendrocrine Processes and Behavior

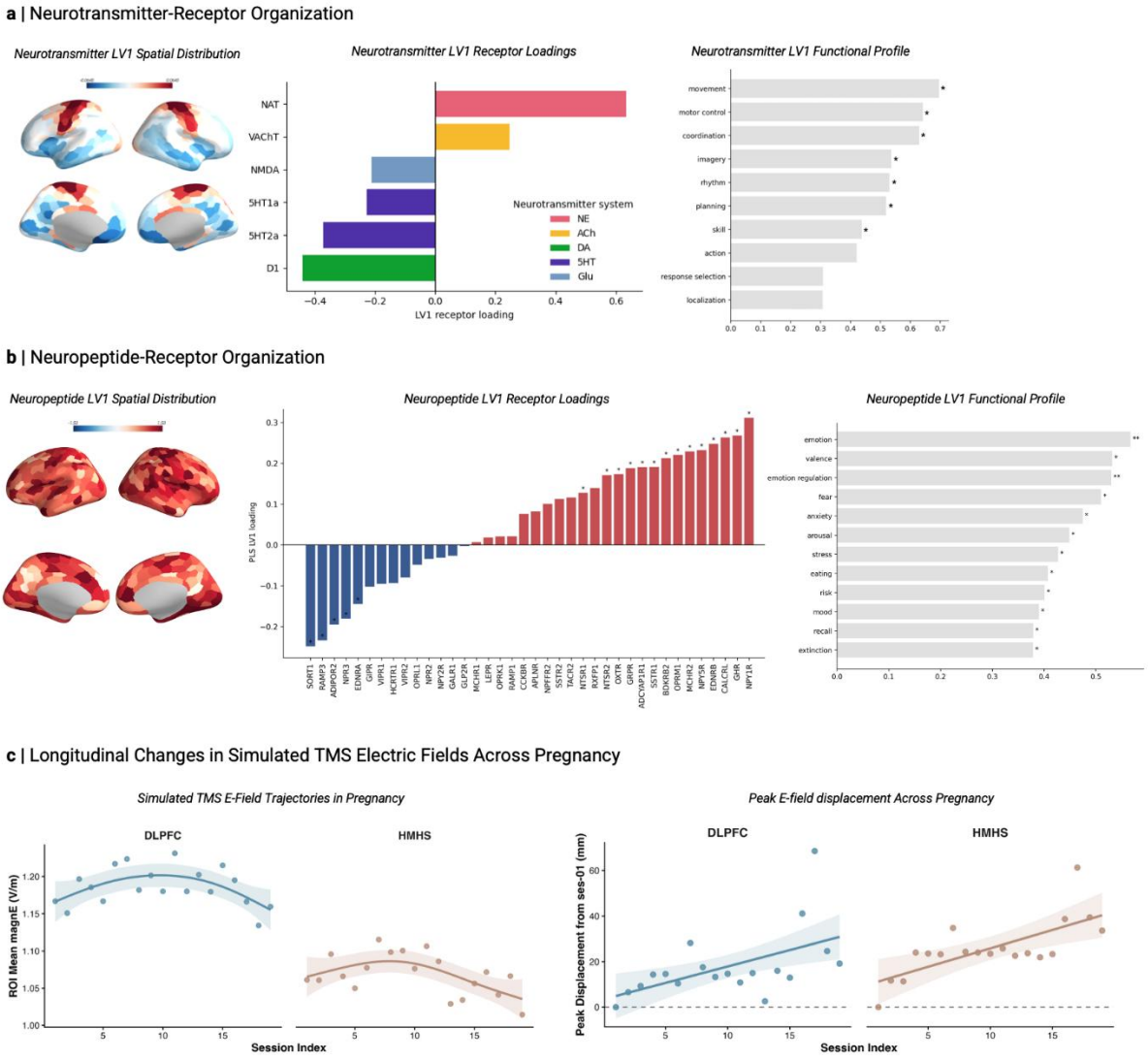
Support: 2023 Career Award for Medical Scientists from the Burroughs Wellcome Fund
Fall 2025 Louis H. Castor, M.D., C'48 College Alumni Society Undergraduate Research Grant

Title: From Neurochemical Architecture to Neuromodulation: Implications of Maternal Brain Remodeling for Precision Psychiatry

Authors: *N. RUBAU APA[1,2], L. PRITSCHET[3,2], C. HAYES[3,2], A. FRANCISCO[3,2], G. SHAFIEI[3], S. SHANMUGAN[3,2,4,5];

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Abstract: The perinatal period is a profound endocrine transition characterized by widespread gray matter volume (GMV) remodeling and increased vulnerability to mood and anxiety disorders. However, the neurobiological basis of this maternal brain plasticity remains poorly understood. To address this gap, here we present preliminary work from two studies investigating the neurochemical organization of pregnancy-related brain remodeling and its effects on modeled neuromodulation target engagement. First, using longitudinal MRI from a nulliparous woman scanned preconception through postpartum (n=26 sessions), we modeled cortical GMV trajectories and quantified pregnancy-related remodeling. We compared GMV change maps to normative neurotransmitter and neuropeptide receptor distributions using mass-univariate (spatial correlation) and multivariate (partial least squares; PLS) analyses. Multivariate analyses identified a latent neurochemical axis linking structural change to coordinated variation across neurotransmitter receptor distributions, associated with motor and action-related functional systems (Fig 1a). Neuropeptide systems showed stronger spatial alignment with cortical remodeling and revealed an axis associated with affective and interoceptive domains (Fig 1b). In a second study, we used this same dataset to model TMS-induced electric fields and examine how pregnancy-related neuroanatomical changes influence neuromodulation target engagement. Despite fixed stimulation parameters, gestational neuroanatomical changes altered electric field magnitude, scalp-to-cortex distance, dose-scaling requirements, and peak stimulation localization (Fig 1c). These findings suggest pregnancy-related brain remodeling reflects coordinated neurochemical architecture and dynamically alters modeled TMS target engagement across gestation. By linking molecular organization, structural remodeling, and neuromodulation, these results provide a framework for future studies of reproductive neuroplasticity and brain-based interventions.



Disclosures: N. Rubau Apa: None. **L. Pritschet:** None. **C. Hayes:** None. **A. Francisco:** None. **G. Shafiei:** None. **S. Shanmugan:** None.

Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.04

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Mapping Risk Across the Postpartum Neuroendocrine Transition: Multimodal Risk Stratification of Postpartum Depression

Authors: *E. BEYDLER;
Penn Psychiatry, Philadelphia, PA

Abstract: The postpartum period is a profound neuroendocrine transition marked by dramatic declines in estrogen, progesterone, and neurosteroid metabolites that reshape affective circuitry and heighten vulnerability to psychiatric disorders. Postpartum depression (PPD) affects approximately 15% of birthing individuals and is the most common complication of childbirth, yet no validated clinical risk model exists to identify at-risk individuals before symptom onset, missing the critical window for primary prevention. Using clinical, electronic health record, and genomic data from the Penn Medicine Biobank encompassing over 10,000 pregnancies (2020-2023), we are developing a clinically interpretable risk stratification model for PPD using within an exposomal framework, integrating multidimensional risk factors across social, demographic, psychiatric, obstetric, and behavioral domains to capture individual-level variation in neuroendocrine burden across the perinatal period. We performed a systematic review and meta-analysis across 101 studies and 19,698 PPD cases, which demonstrated that genome-wide association study (GWAS)-derived polygenic risk scores (PRS) were significantly associated with PPD (OR = 1.55, $\beta = 0.44$, $p < 0.001$), accounting for 3-8% of variance, yet effect sizes were substantially smaller than clinical factors, including prior depressive episode (OR = 4.0, $\beta = 1.39$, $p < 0.001$) and prenatal depression (OR = 9.2, $\beta = 2.20$, $p < 0.001$). PPD was further shown to be genetically heterogeneous: hormonal pathway PRS predominated in early-onset PPD (0-6 months), MDD-pathway PRS in late-onset PPD (6+ months), and inflammatory and circadian PRS distinguished unipolar from bipolar depression subtypes. Critically, 98% of participants across included studies were of European ancestry, limiting generalizability. Building on this, we are integrating GWAS-derived PRS using cross-ancestry analysis to test whether genomic risk (reflecting inherited differences in neuroendocrine sensitivity) improves prediction above clinical factors alone, and applying unsupervised clustering to characterize empirically derived subtypes in this larger, more ancestrally diverse sample. These findings aim to establish a population-scale framework for mapping neuroendocrine vulnerability to PPD, with direct implications for precision prevention during the postpartum transition.

Disclosures: E. Beydler: None.

Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.05

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH R01MH120313

Title: Differential correlations between pregenual anterior cingulate cortex resting state connectivity and GABA+ concentrations in major depressive disorder with antepartum onset vs. healthy postpartum females

Authors: *K. M. DELIGIANNIDIS, MD[1], A. D. BARBER[1], X. HE[2], H. CAO[1], M. JOHN[1], S. JACOB[3], A. GIANNOPOULOS[3], H. MONSIVAIS[4,5], G. NOSSA[6], B. BOZYMSKI[7,5], U. DYDAK[5,8];
[1]Feinstein Inst. for Med. Res., Manhasset, NY; [2]Physics, Hofstra Univ., Hempstead, NY; [3]Psychiatry, Zucker Hillside Hospital, Northwell Hlth., Glen Oaks, NY; [4]The Univ. of Texas at MD Anderson Cancer Ctr., Houston, TX, ; [5]Purdue Univ. Sch. of Hlth. Sci., West Lafayette, IN; [6]Ctr. for Biomed. Imaging, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [7]Radiation Oncology, Univ. of Michigan, Ann Arbor, MI; [8]Radiology and Imaging Sci., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Background: Major depressive disorder with peripartum onset (PPD) affects 1 in 10 birthing females. Altered neuroactive steroid-dependent GABAergic functioning/neuroplasticity in affective neurocircuits is part of an integrated hypothesis for PPD pathophysiology. PPD is characterized by default mode network (DMN) hyperactivity. Since resting-state GABA+ concentrations are associated with functional connectivity within and between resting-state networks and DMN BOLD responses are mediated by GABA, we examined the relationship between DMN GABA+ and DMN network dysfunction in PPD. We hypothesized DMN connectivity would correlate with GABA+ concentrations and depression severity in PPD, and that this correlation would be specific to DMN connectivity and absent in a comparison network. **Methods:** In this interim analysis of R01MH120313, resting-state fMRI scans were acquired on a 3T SIEMENS Prisma. 1H-MRS ROIs were placed midsagittally in the pgACC and a comparison region, the occipital cortex (OCC). GABA-edited spectra were acquired using MEGA-PRESS. Using 5mm spheres centered within MRS ROIs, time series for seed regions were extracted. Full-brain connectivity maps were submitted to Fisher r-to-Z transformation and entered into SPM group models testing for associations with connectivity, depression severity and GABA+. **Results:** 49 participants (mean age 33.32, SD=4.89) completed postpartum imaging (mean days postpartum=59.30, SD=17.31). pgACC GABA+ was positively correlated with pgACC-precuneus/posterior cingulate cortex connectivity in PPD (n=21). Connectivity between these regions positively correlated with HAMD17 ($p=0.008$). In healthy postpartum females (n=27), pgACC GABA+ was negatively correlated with pgACC-precuneus/posterior cingulate connectivity ($p<0.01$). In PPD (n=19), OCC GABA+ was negatively correlated with OCC-pgACC connectivity ($p<0.001$) but positively correlated in healthy postpartum females (n=30, $p<0.001$) and was not correlated with HAMD17 ($p>0.05$). **Conclusions:** This study provides first evidence that pgACC GABA+ concentrations are positively correlated with DMN resting-state connectivity in PPD and negatively correlated in healthy postpartum females. These correlations differed in directionality in the visual network, a comparison region lacking a relationship to depression severity. This analysis suggests the importance of pgACC GABAergic dysfunction within the DMN in PPD and supports integrated RSFC and MRS approaches to understand the functionally specific role of GABA within networks and their relationship with PPD.

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Nanosymposium

NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

Location: WCC Rm 144

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO34.06

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Longitudinal in vivo two-photon imaging of hippocampal spine density across pregnancy and postpartum reveals dynamic structural remodeling

Authors: *A. J. ZULCH[1], N. WOLCOTT[3], E. G. JACOBS[4], M. J. GOARD[2];
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Abstract: Pregnancy is a major hormonal and physiological transition associated with changes in cognition, affect, and risk for mental health disorders such as perinatal depression and anxiety. Human neuroimaging studies have revealed robust pregnancy-related alterations in brain structure, yet the cellular mechanisms underlying these changes remain poorly understood. Because the hippocampus is highly sensitive to hormonal fluctuations and supports learning, memory, and affective processes, we used longitudinal in vivo two-photon imaging through implanted glass microperiscopes to track spine density of the same dendritic segments of CA1 pyramidal neurons every other day across baseline, pregnancy, and postpartum in six female mice. This within-neuron, within-subject design enabled repeated measurement of hippocampal synaptic structure across the full reproductive transition. Dendritic spines, the principal sites of excitatory synapses, provide a structural measure of synaptic connectivity and circuit remodeling. Relative to baseline, dendritic spine density increased by 21% during pregnancy and declined by 15% at parturition, revealing pronounced and temporally precise remodeling of hippocampal synaptic structure across pregnancy and postpartum. Longitudinal imaging has also been initiated in mice with localized CA1 ERα knockdown to investigate the contribution of estrogen signaling to pregnancy-associated synaptic remodeling. Together, these findings establish pregnancy as a period of dynamic hippocampal synaptic plasticity and provide a foundation for investigating the hormonal mechanisms that govern brain remodeling across reproductive transitions.

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NANO34: The Maternal Brain: Plasticity in Brain and Behavior Across the Reproductive Lifespan

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Presentation Number: NANO34.07

Topic: G.02. Neuroendrocrine Processes and Behavior

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Title: Early life stress impacts the risk for peripartum affective dysfunction from genes to behavior

Authors: M. NICODEMUS, ***K. E. MORRISON**;
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Abstract: Women are at increased risk for mood and anxiety disorders, although this risk is heterogeneous and manifests uniquely across the lifespan. Two known risk factors are stress during puberty and later becoming pregnant. Although early life stress is associated with increased risk for perinatal mood and anxiety disorders, we understand little about the mechanisms underlying the enduring risk from either of these factors individually or when they are combined. Pubertal stress is associated with a blunted glucocorticoid response in peripartum humans and mice. Our recently published work shows that pubertally stressed mice respond negatively to the increased allopregnanolone levels of pregnancy, suggesting that the hormonal changes of pregnancy may be detrimental in females with a history of early life adversity. Here, we utilized our mouse model to further understand the effects of pubertal adversity on peripartum behavior, physiology, and gene expression in the brain. In all studies, mice were exposed to chronic variable stress (CVS) from postnatal day 21-34 using our established paradigm or were left undisturbed (Control). In one study, adult females were bred and were repeatedly tested for their behavioral and hormonal response to novel pups at 1.5, 9.5, and 17.5 days post-conception (dpc; early, mid, and late pregnancy). We found a significant effect of pubertal stress on the corticosterone response to novel pup retrieval that interacted with stage of pregnancy. Additionally, the maternal behavior in pubertally stressed females become progressively disorganized. In another study, factors that are known stressors were systematically varied during pregnancy: housing density, repeated testing, and nesting resources available. Mice were tested for maternal behavior, depressive- and anxiety-like behavior (sucrose preference test, splash test, open field test, social interaction test), and corticosterone response to pup retrieval. CVS females showed alterations to sucrose preference and grooming in the splash test, and CVS females exposed to increased stress during pregnancy show a longer latency to engage with pups, but faster retrieval once maternal behavior sequence begins. The corticosterone response was also influenced by pubertal stress and degree of stress during pregnancy. We are also examining the transcriptome of two key hypothalamic regions, the medial preoptic area, which is involved in the expression of maternal behavior, and the paraventricular nucleus, which regulates the hormonal stress response. These studies provide insight into the complex risk factors that interact in the lifespan to produce negative outcomes for females.

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Title: Suprachiasmatic nucleus neuroplasticity during pregnancy as a potential driver of increased sensitivity to light at night in the mouse

Authors: *H. M. HOFFMANN, S. VELAMURU, N. CINTRON, F. RAMOS, A. SMITH, A. M. YAW;
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Abstract: Pregnancy induces adaptations throughout the maternal brain and body to support fetal growth. These adaptations extend to the suprachiasmatic nucleus (SCN), the master circadian pacemaker of the brain, which coordinates daily rhythms in physiology. Previous studies demonstrated that pregnancy alters circadian variables, including locomotor activity and body temperature, suggesting that the maternal circadian system undergoes functional reorganization. However, the neural mechanisms underlying SCN plasticity during pregnancy remain poorly understood. Vasoactive intestinal peptide (VIP)-expressing neurons of the SCN are of particular interest because they receive direct retinal input, synchronize SCN neuronal networks, and are critical mediators of light-induced phase resetting, which regulates light-at-night and shiftwork-like light exposure-induced changes to neuroendocrine function. To investigate pregnancy-induced changes in the maternal circadian system, we examined locomotor rhythms, photic entrainment, and SCN VIP expression during mouse pregnancy under stable light dark conditions and an irregular light-dark (iLD) cycle that mimics a shiftwork-like lighting paradigm. To assess SCN free-running period, we placed females in constant darkness. Compared to virgins, pregnancy and pseudopregnancy caused significant gestation day (GD) specific changes in free-running period, indicating a core role of progesterone in regulating SCN output. Using transgenic circadian PER2::luciferase reporter mice, we found that progesterone lengthened PER2 period in SCN explants at GD18. We also identified a mid-gestation reduction in VIP in the SCN, followed by a significant increase at term. To determine how these SCN changes impacted photic entrainment, we subjected virgin, GD5, and GD15 females to a 1h light pulse during the dark cycle. GD5 and GD15 females exhibited increased phase-shifts compared to virgin females. This increased photic entrainment of pregnant females was further supported by altered entrainment of iLD pregnant females, as compared to virgins. Importantly, iLD during pregnancy caused a proinflammatory status in the mother and lead to over 40% of the females having labor dystocia, as compared to none of the females on a stable LD cycle. Together these data identify dynamic regulation of VIP expression and altered photic responsiveness during pregnancy. These adaptations may represent an important mechanism through which the

maternal brain coordinates physiological and behavioral changes required for successful pregnancy and highlights the consequences of iLD on pregnancy outcome.

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Title: Maternal motivation overcomes innate fear via prefrontal switching-ramping dynamics

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Abstract: Unlike structured decision-making tasks, action selection in naturalistic contexts is usually on a moment-to-moment basis, accompanying spontaneous fluctuation of intrinsic motivation. Such spontaneity is further modulated by distinct cues to bias behaviors. However, neural mechanisms underlying spontaneous action selection remain unknown. Here we report a semi-naturalistic risk-taking maternal behavior paradigm, in which maternal altruism facilitated a female mouse overcoming fear of heights to retrieve the offspring. In this paradigm, conflicting cues result in fluctuating motivation and spontaneous transitions between defensive and pup-oriented behaviors. We found that a prefrontal-midbrain circuit is specifically essential to altruistic control of fear, but not the fear itself, or selfish motivation that overcomes fear. Representational geometry and switching-ramping dynamics in the circuit allow for integration of conflicting cues to influence fluctuation of risk-taking maternal motivation. Our results provide mechanistic insights into behavioral dynamics in naturalistic contexts, and uncover circuit basis for altruistic control over innate fear.

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Title: Hippocampal Tissue Mechanics Track Estrogenic Fluctuation: A Mechanobiological Framework Linking MRE to ERα and Piezo1 Signaling in Female Rats

Authors: *K. A. MILBOCKER[1], S. S. VANDER WIELE[1], L. T. WILLIAMS[1], K. PENNA[2], M. BISCHOFF[3], J. ABREU MIRABAL[3], S. S. INDRAKANTI[3], A. Y. KLINTSOVA[3], C. L. JOHNSON[1];
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Abstract: Estrogenic fluctuations modulate cell mechanobiology in peripheral tissues in women, yet their influence on brain tissue mechanics is unexplored. Given that sex steroid hormones significantly remodel brain microstructure, we hypothesized that estrogenic fluctuation similarly drives mechanobiological changes in brain tissue measurable by magnetic resonance elastography (MRE). MRE is an imaging technique that quantifies tissue viscoelastic mechanical properties from displacement fields generated by applied vibrations. This work aimed to mechanistically test whether estrogen production alters brain tissue mechanics, validated with histology, with implications for women's brain health.Female Long-Evans rats exhibiting regular estrous cycles underwent anesthetized MRE scanning during each cycle phase and following disruption of α estrogen receptor signaling via treatment with the antagonist Fulvestrant. A custom MRE sequence was employed on a 9.4T Bruker MRI system with mechanical vibration achieved via a piezoelectric actuator coupled to a bite bar. Tissue stiffness and damping ratio were computed from displacement data using boundary-condition-free nonlinear inversion. Immunofluorescent quantification of estrogen (ERα) and Piezo1 receptor expression on glia was assessed using unbiased stereology. Piezo1 transduces mechanical stimuli into biochemical signals; its role in hormone-related brain mechanobiology is unexamined.Hippocampal damping ratio increased by 39% between proestrus and estrus phases as estrogen naturally declined (p=0.028). Fulvestrant treatment abolished this phase-dependent shift in damping ratio (p=0.326), suggesting that estrogenic signaling is necessary for cycle-related changes, and reduced astrocyte (p=0.004) and neuron (p=0.007) number relative to controls. ERα expression was elevated on remaining astrocytes (p=0.021). We hypothesize that this reflects translocation of ERα from the nucleus to the cell membrane, a shift that may alter membrane viscoelasticity and will be validated with histology. Because astrocytes serve as primary structural organizers of brain tissue, changes in their individual stiffness are predicted to propagate to the tissue level.

Piezo1 co-labeling will test whether this altered mechanical microenvironment is sensed by neighboring cells.These findings reframe the female brain as a mechanodynamic organ whose structural properties are continuously tuned by hormonal state. This framework may elucidate why cognition and broader nervous system homeostasis are disrupted during hormonal transition phases with implications for brain health across the lifespan.

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Title: Median preoptic EP3R/NK3R neurons underlie vasomotor symptoms

Authors: *N. LYNCH[1], L. ANGENENDT DA COSTA[2], A. KELLY[1], C. E. MAHONEY[1], C. B. SAPER[1], N. L. MACHADO[1];
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Abstract: Vasomotor symptoms (VSM) affect up to 80% of menopausal women, profoundly impacting quality of life and have been associated with an increased risk of cardiovascular disease, stroke, and cognitive decline in aging, yet the neural circuits driving them remain almost entirely uncharacterized. During menopause, sudden and dramatic decreases in circulating estrogen levels are hypothesized to lead to unopposed overactivation of neurokinin 3 receptors (NK3R) in the median preoptic nucleus (MnPO) due to the exaggerated release of neurokinin B, triggering VSM. Building on our prior identification of EP3R-expressing MnPO neurons that function as a thermoregulatory switch, we hypothesized that co-expression of MnPO-EP3R and -NK3R defines a population both necessary and sufficient for VSM generation. Previous single-cell RNA sequencing studies and our ISH work confirmed substantial molecular overlap of these receptors in the MnPO. Fiber photometry revealed that MnPO-EP3R neuron activity was significantly increased following senktide compared to saline (AUC: 1664.2 ± 290.1 vs 486.3 ± 286.4 ΔF/F; $p = 0.001$), with neural activation preceding core body temperature (Tb) drop by 9.3 minutes ($p = 0.0001$). MnPO-EP3R cell-specific ablation abolished senktide-induced Tb decrease (WT vs EP3R-ablated: $p = 0.0016$), while optogenetic inhibition significantly attenuated it (−2.56 ± 0.38°C vs −0.61 ± 0.27°C; paired t-test, $p = 0.013$). Identifying the

dorsomedial hypothalamus as a key downstream target using circuit tracing, MnPO-EP3R terminal inhibition in this region also produced a significant attenuation of senktide-induced Tb decrease (−3.01 ± 0.2°C vs −1.98 ± 0.16°C; paired t-test, p = 0.0006). Aged mice show reduced MnPO-EP3R and -NK3R expression, disrupted circadian temperature rhythms, and blunted senktide response, mirroring the MnPO-EP3R ablation phenotype and further implicating this population in age-related thermoregulatory decline. Together these findings identify the neural locus of hot flush generation, establish a circuit framework for VSM generation, and provide a mechanistic basis for targeting thermoregulatory dysfunction across menopause and aging.

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Nanosymposium

NANO35: From Neurons to Narratives: Multimodal Approaches to Human Affect

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Presentation Number: NANO35.01

Topic: H.04. Emotion

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Title: Characterization of personalized Affective States by Utilizing Large Human Multimodal Neurophysiological Datasets

Authors: *M. BIJANZADEH[1], B. NANDI[3], R. CAMPUSANO, Jr.[2], J. D. TOWNSEND[4], V. WANG[5], I. HARTLEY[2], M. OSHEROFF[6], A. GAZZALEY[2], T. P. ZANTO[2], R. ABBASI-ASL[7];
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Abstract: Emotional experience is deeply personal, manifesting through unique behavioral patterns and neurophysiological changes. These changes arise from complex interactions between distributed brain regions and the autonomic nervous system (ANS), further shaped by factors such as sleep, circadian rhythms, and nutrition. When these systems disharmonize, affective disorders such as depression and anxiety can emerge. Machine learning (ML) combined with large-scale, within-individual datasets offer an objective framework for probing personalized biomarkers that conventional population-level averaging obscures. To investigate individualized markers of emotion, we collected one of the most comprehensive multimodal biosensing datasets in affective research from five participants across four 1-hour sessions, yielding 168 one-minute trials per participant. Using a 128-channel EEG system and 28

peripheral physiological sensors (EMG, ECG, EDA, etc.), we recorded brain and ANS responses as participants viewed emotionally evocative videos and provided subjective emotion ratings. From 102 spectral EEG and ANS features (i.e., alpha and theta power, heart rate variability, tonic and phasic EDA, diastolic and systolic blood pressure, respiration rate, radial blood flow), normalized within recording blocks to control for drift, and using interpretable ML models (i.e., elastic-net logistic regression and random forests) with rigorous block-wise cross-validation, we accurately classified all 15 discrete emotions from baseline no-stimulus states with consistently high discrimination. We then ranked the predictive contribution of every feature per emotion using model coefficients and grouped these predictors by their mutual correlations into physiologically coherent clusters whose number was selected by silhouette analysis. We further grouped emotions by their common and distinct neurophysiological features, and separately by self-reported ratings. Network analyses then probed the clustering consensus between self-ratings and neurophysiological features, identifying which emotions are consistently recovered across both modalities, and characterized the feature clusters associated with each consensus group. For example, medial frontal alpha was a common feature across emotions but unimportant for aesthetic appreciation, which frontal gamma and alpha dominated. Zygomaticus changes dominated most emotions, except boredom, and weakly for calmness and entrancement. This experimental and computational framework offers individualized, objective emotional indicators within both the brain and body, aiding personalized diagnosis.

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Nanosymposium

NANO35: From Neurons to Narratives: Multimodal Approaches to Human Affect

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO35.02

Topic: H.04. Emotion

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Title: A causal and lateralized role of the human amygdala in evidence accumulation under emotional ambiguity

Authors: *S. SUN[1,2], T. XIE[3], S. WANG[3], P. BRUNNER[3], J. T. WILLIE[2];
[1]Tohoku Univ., Sendai, Japan; [2]The Univ. of Texas at Austin, Austin, TX; [3]Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Background: Accumulation-to-bound theories propose that decisions emerge through the gradual integration of noisy evidence toward a decision threshold. Although corticostriatal circuits have been widely implicated in evidence accumulation (EA), the role of the amygdala remains poorly understood. Single-unit recordings suggest that amygdala neurons encode EA signals, whereas neuroimaging studies indicate hemispheric specialization in processing emotional valence and decision ambiguity. However, the causal contribution of the amygdala to EA and its potential lateralization remain unclear. **Methods:** We combined intracranial electrophysiological recordings (n=15), direct electrical stimulation of the amygdala (n=14 sessions), and focal radiofrequency ablation (RFA; n=7) in neurosurgical patients. Participants completed an emotion interpretation task involving graded perceptual ambiguity. EA was quantified using drift diffusion modeling of choice and reaction time data. Amygdala event-related potentials (ERPs) were analyzed to characterize emotional representations and their relationships with latent EA parameters. Stimulation and RFA were used to test the causal role of amygdala hemispheres and subregions. **Results:** Computational-neural mapping analyses revealed that amygdala ERP activity occurring 300-500 ms after face onset tracked trial-by-trial drift-rate estimates, identifying a neural signature of EA within the human amygdala. This effect exhibited nuclei- and hemisphere-specific organization: the left amygdala, particularly the lateral and basal nuclei, encoded both emotional valence and ambiguity and showed robust drift-rate representations, whereas the right amygdala primarily encoded ambiguity and exhibited weaker drift-rate modulation, especially in the lateral nucleus. Consistent with these findings, left amygdala stimulation increased drift rate, whereas right amygdala ablation reduced drift rate, providing causal evidence that the amygdala contributes to EA during social-emotional decision-making. **Conclusions:** These findings provide convergent electrophysiological and causal evidence that the human amygdala contributes directly to evidence accumulation during social-emotional decisions. Our findings extend computational models of decision-making beyond corticostriatal circuits and identify amygdala subnuclei as potential neuromodulation targets for emotional and decision-making dysfunction in psychiatric disorders.

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Presentation Number: NANO35.03

Topic: H.04. Emotion

Title: Neural Correlates of Positive Feelings under Psilocybin: A Personalized Within-Subjects Neuroimaging Study with Healthy Volunteers

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Abstract: Psilocybin is a serotonergic psychedelic that induces a profound altered state of consciousness that appears to mediate rapid and sustained mental health improvements across a broad spectrum of individuals. Prior work has shown that positive emotions, emotional release, and psychological insight are strong mediators of long-term positive mental health changes. However, the neuronal signatures of these pertinent substates—both within a dosing session and across sessions and individuals—remain incompletely understood. To address this, we implemented a deep-sampling multimodal (EEG and fMRI) neuroimaging study in up to fourteen healthy, psychedelic-experienced volunteers receiving 10-25 mg of oral psilocybin across four dosing visits. On each visit, up to 3 hours of eyes-closed resting fMRI data and 28 minutes of EEG data was acquired. Three 15 min fMRI runs and one 7-minute EEG recording were acquired before dosing, and again at 50, 120, and 190 minutes post-dosing. During each fMRI run, participants reported positive versus negative feelings, insight, and acceptance using a 4-button box. Normalized global signal complexity (NGSC), an index of the unpredictability of brain activity, increased at 50 minutes, peaked at 120 minutes, and declined by 190 minutes post-dose relative to baseline. Positive feelings and insight showed a similar temporal profile, peaking at 120 minutes, and correlated with NGSC increases in a distributed network spanning fronto-insular brain regions. When looking at the within-fMRI prompts, positive feeling predicted NGSC in the insula, amygdala, and anterior cingulate. These neural correlates where distinct from those for insight, which was characterized by increased NGSC in the prefrontal cortex. These findings highlight the potential to type psychedelic substates across time and individuals, highlighting increased brain complexity as a marker of psychedelic-induced states of positive affect and insight.

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Title: Integrating multimodal autonomic signals to track affective dynamics during the acute effects of N,N-dimethyltryptamine

Authors: ***T. D'AMELIO**[1,2,4,5], T. GIL GARBAGNOLI[3], J. RODRIGUEZ CUELLO[7], E. LEWIS-HEALEY[8,9,10,11], C. PALLAVICINI[12,2,14], F. CAVANNA[12], N. BRUNO[12,15,2], L. A. DE LA FUENTE[13,2,16,17], S. MÜLLER[12,2], T. A. BEKINSCHTEIN[18], D. VIDAURRE[19,6,20], E. R. TAGLIAZUCCHI[12,21,22];
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Abstract: Serotonergic psychedelics induce altered states of consciousness characterised by profound changes in emotional experience. Although psychedelics modulate autonomic arousal, sympathetic engagement during their affective effects remains poorly characterised. We recorded cardiac, electrodermal, and respiratory activity in 19 participants following inhalation of 20 or 40 mg of freebase N,N-dimethyltryptamine (DMT) under a semi-naturalistic blinded design, alongside time-resolved retrospective phenomenological reports. DMT induced robust increases across all autonomic markers, integrated into a multimodal index that selectively tracked subjective emotional intensity. Dose-dependent divergence followed modality-specific profiles: heart rate and respiratory differences emerged within the first 2 min post-inhalation, whereas electrodermal activity diverged only during the later phase, with higher doses showing prolonged autonomic engagement. DMT thus produces a transient sympathetic activation co-varying with emotional arousal, followed by gradual disengagement accompanied by pleasantness and bliss. By combining time- and cost-effective peripheral physiological measures with time-resolved phenomenological reports, this work contributes to the objective characterisation of psychedelic-induced affective states and provides a methodological basis for future biomarker research in clinical applications.

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Topic: H.04. Emotion

Support: Virginia Tech Institute for Society, Culture and Environment research award.

Title: Parent Internalizing Shapes the Link Between Parent-Child Latent Brain-State Similarity and Child Recent Negative Affect

Authors: *Q. LI, Y.-Y. CHEN, T.-H. LEE;
Dept. of Psychology, Virginia Tech., Blacksburg, VA

Abstract: Parent-child similarity is often interpreted as a marker of attunement, but its developmental meaning may not be uniformly positive. Prior work has shown that this association is conditioned by general family-level factors such as cohesion; here we tested whether a more specific context, the individual parent's own emotional and regulatory profile, shapes what neural similarity means for the child. We further move beyond scan-averaged similarity to examine latent brain-state dynamics that may be obscured by temporal averaging. We analyzed 32 parent-youth dyads, applying a hidden Markov model (HMM-MAR; K=6 states, lowest free energy across K=4-12) to whole-brain ROI timeseries (232 ROIs) while the parent and child separately watched the same emotional film (~14 min). Real dyads showed greater latent similarity than parent-shuffle null pairs on occupancy KL divergence ($t(31)=-3.12$, $p=.004$) and dwell-time correlation ($r=0.44$, $t(31)=6.06$, $p<.001$). Parent internalizing (z-mean of trait/state anxiety, depression, negative affect; alpha=. 92) alone was only a marginal predictor of child recent negative affect ($r=.31$, $p=.085$) and was not correlated with similarity ($r=-.001$, $p=.995$). However, children whose brain-state distributions resembled their parents' showed higher negative affect when the parent reported higher internalizing, but not lower (beta=5.62, $p=.018$; delta-R^2=15.7%). The same interaction emerged when the parent measure was replaced by parent neural-state unpredictability (Htrans), the Markov entropy rate of the parent's state sequence (beta=5.95, $p=.004$), ruling out questionnaire-neural method artifacts. Construct validation across 35 parent measures showed 90% associated with Htrans in the maladaptive direction. Parent self-report alone was only a marginal predictor, whereas the neural similarity interaction added explanatory variance. These findings suggest that dyadic neural similarity should be interpreted in context. Similarity to a parent’s affective-processing profile may be associated with risk as well as adjustment, depending on the parent’s own regulatory profile.

Disclosures: Q. Li: None. **Y. Chen:** None. **T. Lee:** None.

Nanosymposium

NANO35: From Neurons to Narratives: Multimodal Approaches to Human Affect

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO35.06

Topic: H.04. Emotion

Support: NIH grant R01MH116026
Animals Australia for a Kinder World

Title: Linking Functional Network Connectivity Patterns to Immune and Empathic Responses in Witnessing Trauma

Authors: *B. KIM LUX[1], T. D. WAGER[2];
[2]Psychological and Brain Sci., [1]Dartmouth Col., Hanover, NH

Abstract: Witnessing trauma can profoundly affect both brain and body. In rodent and human studies, observing another's suffering triggers sympathetic arousal and pro-inflammatory responses, and chronic vicarious trauma can lead to PTSD-like symptoms. Yet, the system-level mechanisms that link these neural, autonomic, and immune changes remain incompletely understood. In this study, viewing animal suffering footage (Vicarious Trauma, VT) generated neural, autonomic, and molecular patterns that differed markedly from those evoked by a positive human-animal interaction documentary (Vicarious Community, VC). Eighty-eight participants watched both films on separate days while undergoing fMRI scan and autonomic monitoring; for a subset of 55 participants, we also performed RNA-sequencing on isolated circulating monocytes to capture innate immune transcriptomic responses. Whole-brain static functional network connectivity (sFNC) was computed from the movie-viewing fMRI data using NeuroMark (105 intrinsic connectivity networks, 5,460 pairwise edges). A linear support-vector-machine trained on the complete edge set discriminated VT from VC with 94.4 % mean accuracy (Cohen's $d = 3.18$) across ten-fold cross-validation repeated ten times. After Bonferroni correction, 439 edges contributed stably to the SVM classification. Using leave-one-subject-out support-vector-regression, the gene expression principal component derived from RNA-seq was estimated from the stable sFNC edges ($r = 0.211, p < 0.05$), indicating that the connectivity pattern captures variance linked to immune activity. Heart rate during movie viewing was also estimated ($r = 0.309, p < 0.0001$), and the empathic concern subscale of the Interpersonal Reactivity Index was estimated from the VT-VC differential sFNC ($r = 0.385, p = 0.004$), while other subscales of IRI did not reach significance. Thus, this study identified a statistically robust set of static functional connections that reliably distinguishes VT from VC. The connectivity pattern is associated with individual autonomic and immune responses to animal suffering and captures empathic traits, establishing a multimodal brain-immune-behavior framework for future translational research.

Disclosures: B. Kim Lux: None. **T.D. Wager:** None.

Nanosymposium

NANO35: From Neurons to Narratives: Multimodal Approaches to Human Affect

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO35.07

Topic: H.04. Emotion

Support: Natural Science Foundation of China (82401432)

Title: Intracranial EEG reveals bidirectional normalization of human pain empathy following slow-paced breathing

Authors: *H.-T. CAI[1,2], P. SUN[3], H. LUO[2];
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Abstract: Pain empathy is essential for social functioning and psychological well-being, yet both excessive and insufficient empathic responses can be maladaptive, contributing to emotional burnout or social deficits. Slow-paced breathing (SPB) represents a promising approach to modulating pain empathy, but its behavioral effect and neural mechanisms remain unclear. Here, we addressed these questions by recording intracranial electroencephalography while participants completed breathing interventions followed by an image-viewing task involving others' pain. We employed a within-subject design in 25 patients with epilepsy (mean ± SD age: 29.28 ± 7.05 years; 16 males). Each participant completed two counterbalanced sessions, with either 5-min SPB or spontaneous breathing followed by the same image-viewing task, while local field potentials (LFPs) were recorded from core empathy-related regions, including the amygdala, anterior insula, temporoparietal junction (TPJ), and anterior cingulate cortex (ACC). Based on pain ratings during spontaneous breathing, the participants were divided into three groups: low, moderate, and high empathy. The results showed that the pain ratings showed a significant breathing condition × empathy subgroup interaction, F (2,975) = 12.84, p < 0.001. Simple-effect analysis showed that SPB decreased pain ratings in high-empathy participants (β = -0.613, $p < 0.001$) while increasing them in low-empathy participants (β = 0.600, $p < 0.001$), suggesting a homeostatic shift of excessive and insufficient empathic responses toward an intermediate range. This behavioral effect was replicated in an independent healthy control sample (n = 27; mean ± SD age: 26.44 ± 7.30 years; 12 males). Intracranial EEG further revealed distinct neural response patterns in high- verse low-empathy participants. High-empathy participants showed a selective increase in ACC theta power during SPB, whereas low-empathy participants showed broader LFP power modulation across all four regions during and after SPB (all FDR-corrected $p < 0.01$). In particular, low-empathy participants showed increased insular power during SPB and decreased amygdala power after SPB within overlapping beta-to-ultra-high-frequency bands, suggesting enhanced interoceptive engagement followed by reduced limbic reactivity. In summary, we have not only identified the bidirectional moderating effect of SPB on pain empathy but have also found that these different moderating effects may depend on distinct brain regions and neural activity.

Disclosures: H. Cai: None. **P. Sun:** None. **H. Luo:** None.

Nanosymposium

NANO35: From Neurons to Narratives: Multimodal Approaches to Human Affect

Location: WCC Rm 146C

Time: Tuesday, November 17, 2026, 1:00 PM - 3:00 PM

Presentation Number: NANO35.08

Topic: H.04. Emotion

Support: Princeton Precision Health
NARSAD Young Investigator Grant, Brain & Behavior Research Foundation, 31386

Title: The valence of client and therapist language reflects symptom changes in messaging-based psychotherapy

Authors: *H. I. VARTIAINEN[1], T. HULL[2], E. C. NOOK[1];
[1]Princeton Univ., Princeton, NJ; [2]Talkspace, New York, NY

Abstract: Natural Language Processing is increasingly used to study mental health, and there are preliminary signs that sentiment (i.e., the valence of one's language) might be an indirect measure of emotion and psychopathology. To provide a robust and naturalistic test of this association, we compared 13 sentiment measures' performance in predicting clients' internalizing symptoms within > 6,000 psychotherapy transcripts. Measures largely converged in showing that client language becomes more positive over time, and that this shift tracks symptom reductions, but subtle differences in performance across measures emerged. These findings can guide future data-driven research on associations between language, affect, and mental health.

Disclosures: H.I. Vartiainen: None. **T. Hull:** None. **E.C. Nook:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

Location: WCC Rm 143

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.01

Topic: I.08. Learning and Memory

Support: SNSF 234622

Title: Hippocampal CA2-CA1 dynamics during social fear extinction

Authors: *P. KASSRAIAN[1], S. A. SIEGELBAUM[2];
[1]Univ. of Bern, Bern, Switzerland; [2]Dept of Neurosci., Columbia Univ. Postdoctoral Dept. of Neurosci., New York, NY

Abstract: When dCA2 pyramidal neurons (PNs) are silenced, mice fail to recall a previously learned discrimination between footshock-associated (CS+) and safe (CS-) individuals and instead display generalized social avoidance (Kassraian et al., Nature Neurosci, 2024). Although repeated, non-reinforced exposure to fearful social stimuli can reduce defensive responses, the hippocampal circuit mechanisms that support this extinction process remain little understood. Here, we find that silencing dCA2 PNs during recall impairs social fear extinction. In contrast, silencing vCA1 PNs reduces freezing around both CS+ and CS- individuals and facilitates extinction, suggesting that vCA1 contributes more directly to the expression of defensive social fear states. To determine how these hippocampal regions encode social information across social fear learning and extinction, we longitudinally tracked dCA2 and vCA1 PN population activity across social fear encoding, recall, and repeated extinction sessions. Social identity could be decoded with high accuracy from both dCA2 and vCA1 PNs within individual sessions, in line with previous work showing that both regions contain robust information about the identity of social stimuli. However, cross-session decoding revealed a dissociation between the two regions: dCA2 identity representations remained relatively stable and generalized across extinction, consistent with social fear conditioning strengthening or stabilizing pre-existing identity-related population structure. In contrast, vCA1 identity representations showed greater session-to-session reorganization across social fear learning and extinction. Consistent with this more state-dependent representation, fear-related behavioral readouts at the individual-subject level were decoded more accurately from vCA1 than from dCA2 population activity. Together, these findings suggest that dCA2 provides a somewhat stable social identity representation, whereas vCA1 more closely tracks defensive state and contributes to the expression of social fear responses that can constrain extinction, that supports memory updating during extinction.

Disclosures: P. Kassraian: None. **S.A. Siegelbaum:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

Location: WCC Rm 143

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.02

Topic: I.08. Learning and Memory

Support: NINDS Competitive Fellowship Award (Intramural F32)

Title: Evoking high-frequency ripple oscillations with direct electrical stimulation improves associative memory in humans

Authors: *U. R. MOHAN[1], D. ZARRIN[5], O. E. FRUCHET[2], Y.-T. A. GAU[3], W. XIE[6], K. K. SUNDBY[7], Y. SERLIN[3], S. INATI[3], K. A. ZAGHLOUL[4];

[1]NINDS, NIH, Washington, DC; [2]Neurosurg., [3]Surgical Neurol. Br., [4]NINDS, NIH, Bethesda, MD; [5]Dept. of Neurosurg., Johns Hopkins Sch. of Med., Baltimore, MD; [6]Dept. of Psychology, Univ. of Maryland, Col. Park, College Park, MD; [7]Psychology, High Point Univ., High Point, NC

Abstract: Effective neuromodulation for memory dysfunction requires understanding both memory-related neural signals and how stimulation modulates them. Intracranial direct electrical stimulation shows promise for treating memory dysfunction, but precise modulation of underlying mechanisms remains poorly understood. Using intracranial electroencephalographic and direct electrical stimulation inneurosurgical epilepsy patients, we investigated how low-amplitudestimulation modulates high-frequency ripple oscillations, neural events underlying memory encoding and retrieval. High-frequency, low-amplitude stimulation trains at hippocampal and cortical sitesincreased local ripple rates in an amplitude-dependent manner, with synchronous ripple patterns emerging in functionally connected regions. We found that ripple activity evoked following microstimulation coincided with temporally organized bursts of spikingactivity, suggesting they may function as physiological memory-related ripples. We applied patterned stimulation during an associative memory task and found participants improved in recall performance by 14.5% relative to unstimulated lists, with gains driven specifically by evoking hippocampal and coordinated ripples between brain regions during memory retrieval. Together, these findings causally link ripple oscillations to human memory and demonstrate, for the first time in humans, that targeting ripples with low-amplitude stimulation can enhance memory performance.

Disclosures: U.R. Mohan: None. **D. Zarrin:** None. **O.E. Fruchet:** None. **Y.A. Gau:** None. **W. Xie:** None. **K.K. Sundby:** None. **Y. Serlin:** None. **S. Inati:** None. **K.A. Zaghloul:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

Location: WCC Rm 143

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.03

Topic: I.08. Learning and Memory

Support: NIMH Grant R01MH135576

Title: Dendritic inhibition and disinhibition gate hippocampal reward over-representation

Authors: *M. FINCH[1], M. VIVIAN[2], L. MARTIN[2], C. GRIENBERGER[2], A. D. MILSTEIN[1]; [1]Dept. of Neurosci. and Biol., Rutgers Univ., Piscataway, NJ; [2]Dept. of Biol., Brandeis Univ., Waltham, MA

Abstract: During spatial learning, hippocampal pyramidal neurons rapidly change their selectivity for features of the environment, with a bias towards over-representing goals and goal-predictive cues. Experimental and theoretical evidence suggest that these adaptations reflect a recently discovered form of plasticity induced by dendritic calcium spikes termed behavioral

timescale synaptic plasticity (BTSP). Dendritic calcium spikes are promoted by excitation of distal dendrites by long-range projections from cortex and limited by local dendritic feedback inhibition. However, it is less understood how these mechanisms interact with other feedforward and disinhibitory circuit elements during learning. Here we use in vivo calcium imaging to investigate the feature selectivity and learning dynamics of a population of NDNF-expressing feedforward dendrite-targeting interneurons. Latent factor analysis suggests that NDNF+ interneurons functionally segregate into subtypes with distinct profiles of modulation by reward and adaptation over learning. Incorporating these inhibitory cells into circuit models of place field formation support important roles for three distinct inhibitory motifs in generating goal representations: feedforward dendritic inhibition by NDNF+ interneurons, feedback dendritic inhibition by SST+ interneurons, and dendritic disinhibition mediated by a suppression of SST+ interneurons at rewards.

Disclosures: M. Finch: None. **M. Vivian:** None. **L. Martin:** None. **C. Grienberger:** None. **A.D. Milstein:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

Location: WCC Rm 143

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.04

Topic: I.08. Learning and Memory

Support: NIMH R01 R01NS116357

Title: Contamination of Engram Coactivity Networks During Forgetting

Authors: *L. AN[1], M. YANG[2], H. WANG[1];
[1]Physiol., Michigan State Univ., East Lansing, MI; [2]Anat., Wonkwang Univ. Sch. of Med., Iksan, Korea, Republic of

Abstract: Forgetting is a fundamental component of adaptive memory and essential for cognitive flexibility, yet its cellular basis remains unclear. Here we establish a mouse model of retroactive interference (RI) and show that post-learning novelty exploration induces active forgetting of hippocampus-dependent object location memory only within a discrete consolidation window defined by protein synthesis sensitivity. RI imposed within this window reduces engram reactivation and destabilizes a structured coactivity network formed during learning. Mice that forget retrieve reorganized engram with increased edge turnover and reduced training edgesurvival during recall. During this vulnerable period, RI infiltrates the engram core, whereas after consolidation it remains confined to the network periphery. Over the consolidation window, the engram network progressively matures, acquiring greater density, similarity, and k-core robustness, features that confer resistance to interference. Importantly, blocking RI infiltration rescues memory formation. Together, these findings show that forgetting arises from

reorganization of engram topology during consolidation and identify engram core contamination as a network-level substrate for forgetting.

Disclosures: L. An: None. **M. Yang:** None. **H. Wang:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

Location: WCC Rm 143

Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.05

Topic: I.08. Learning and Memory

Support: NIH Grant R01

Title: Newly mature hippocampal neurons actively maintain remote memory fidelity

Authors: *T. X. PHAN[1], P. KUMAR[1], M. GUPTA[2], A. LEOW[3], O. LAZAROV[1];
[1]Anat. and Cell Biol., [2]Biomed. Engin., [3]Psychology, Univ. of Illinois Chicago, Chicago, IL

Abstract: While adult-born neurons (ABNs) are known for encoding new memories, their role in preserving memory fidelity over time is unresolved. Here, we show that a specific cohort of newly mature ABNs is causally indispensable for maintaining the specificity of remote contextual memories. Using chemogenetics, we found that prolonged (24-hour), but not acute, silencing of these ABNs within a critical post-retrieval window severely impairs remote context discrimination. This requirement for sustained ABN activity is mechanistically distinct from classic protein-synthesis-dependent reconsolidation. Calcium imaging revealed the underlying neuro-computational mechanism: ABN silencing degrades the population code by collapsing the orthogonality of neural representations for similar contexts, which we attribute to a narrower range in the neural population code's repertoire without the participation of ABNs. These findings establish a new principle of memory biology: newly mature ABNs act as 'fidelity guardians,' ensuring the precision of remote memories through a process of continuous, active maintenance of population code integrity.

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Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

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Time: Tuesday, November 17, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO36.06

Topic: I.08. Learning and Memory

Support: NIH-NINDS 2R01NS089729

Title: Dissociable prospective codes in CA3/DG and CA1 during learning of overlapping routes

Authors: *S. MIRJALILI[1], W. GUO[4], L. I. RAIT[1], E. WANG[5], K. L. HEDMAN[1], U. MAYR[2], B. A. KUHL[3];
[2]Psychology, [3]Psychology Dept., [1]Univ. of Oregon, Eugene, OR; [4]Psychology, Princeton Univ., Princeton, NJ; [5]Dept. of Psychology, USC, Los Angeles, CA

Abstract: The hippocampus plays a critical role in disambiguating overlapping spatial routes. In fact, recent human fMRI studies have found that hippocampal representations of overlapping routes are more distinct (lower pattern similarity) than representations of non-overlapping routes (Wanjia, Han, et al., 2025; Chanales, Oza, et al., 2017). This finding suggests that overlap triggers a 'repulsion' of hippocampal representations. However, it is not clear to what degree this repulsion reflects prospective information about future route paths (e.g., Pfeiffer & Foster, 2013; Johnson & Redish, 2007) versus discrimination of current perceptual input. Here, we used a naturalistic route-learning paradigm that required participants (N = 38, ages 18-30) to predict their destination as early as possible. Each route consisted of three segments separated by left/right turns. Critically, overlapping routes shared the first two segments and diverged at the second turn. We defined the first turn as 'decision point 1' and the second turn as 'decision point 2'. With practice, participants learned to discriminate the overlapping routes with 90% accuracy by decision point 1 (well before the routes actually diverged). Using high-resolution fMRI, we next examined anticipatory representations in hippocampal subfields by comparing neural representations across the two decision points. Strikingly, at decision point 1, CA3 and dentate gyrus (CA3/DG) showed a prospective repulsion effect: lower pattern similarity to decision point 2 of the overlapping route than to decision point 2 of non-overlapping routes ($P < 0.001$). In other words, CA3/DG differentiated current states from competing future states. This prospective repulsion effect was absent in CA1 ($P = 0.318$). Instead, CA1 showed a prospective representation of the target route: pattern similarity between decision points 1 and 2 (of the same route) was higher than pattern similarity between decision points 1 and 2 of non-overlapping routes ($P = 0.041$). Finally, while CA3/DG and CA1 each exhibited prospective effects that related to key decision points, they did not code for the route's destination ($P's > 0.278$). In contrast, orbitofrontal cortex showed destination coding ($P = 0.023$) that emerged at the same time as the hippocampal prospective effects. Together, these findings reveal dissociable prospective codes that differentiate competing trajectories, bridge successive states, and maintain goal representations.

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Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

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Presentation Number: NANO36.07

Topic: I.08. Learning and Memory

Support: NIH R01 MH129436
NIH RF1 NS127128

Title: A mixture-of-experts model of hippocampal-mPFC interactions

Authors: *D. SINGH[1], A. C. SCHAPIRO[2];
[1]Princeton Univ., Princeton, NJ; [2]Psychology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The hippocampus supports both memory for individual experiences and extraction of shared structure across experiences, despite the competing computational demands of pattern separation and integration. Prior work suggests that these functions may depend on distinct hippocampal pathways: the trisynaptic pathway (TSP), which builds sparse pattern-separated representations suited to episodic specificity, and the monosynaptic pathway (MSP), which builds overlapping representations suited to statistical learning. A fundamental mystery remains, however: how does the brain recruit the right representation at the right time? Evidence that medial prefrontal cortex (mPFC) exerts task-specific control over hippocampal outputs suggests one possible mechanism. We introduce a stimulus-computable mixture-of-experts model in which sensory representations are transformed by MSP- and TSP-like neural network experts under the control of an mPFC-inspired gating network that computes trial-wise mixture weights over their contributions. In Simulation 1, the model was trained on Fashion-MNIST category and exemplar labeling tasks. Learned gating preferentially recruited MSP for category learning but shifted almost entirely to TSP for exemplar learning. Within category learning, more prototypical items elicited greater MSP recruitment, whereas atypical items depended more on the TSP. In Simulation 2, the model captured mPFC lesion-sensitive fear-memory specificity in a rodent contextual fear-conditioning paradigm: intact mPFC gating supported selective discrimination of the shock context, whereas disabling the gate produced overgeneralization to similar contexts. Mechanistically, intact gating preserved TSP pattern separation of the shock context, whereas disabling the gate reduced separation between shock and similar contexts, accounting for the overgeneralization. In Simulation 3, simulating human category learning, the model reproduced graded behavioral generalization to novel category members, while the mPFC gate tracked prototype structure in a manner consistent with reported vmPFC neural signatures, suggesting that abstract category sensitivity may emerge in the service of control over hippocampal representations. Together, these findings suggest that mPFC-like gating can determine which mnemonic format is expressed in hippocampal output — MSP-mediated representations of shared structure or TSP-mediated representations of episodic specificity, providing a mechanism by which transformed memory representations can be flexibly deployed to guide behavior.

Disclosures: D. Singh: None. **A.C. Schapiro:** None.

Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

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Presentation Number: NANO36.08

Topic: I.08. Learning and Memory

Support: NIH R01MH069456

Title: Hippocampal-cortical interactions supporting differentiation of similar memories over time

Authors: *I. ZHOU[1], E. A. MCDEVITT[5], I. H. QURAISHI[2], E. C. DAMISAH[3], K. A. NORMAN[5,6], N. B. TURK-BROWNE[1,4];
[1]Psychology, [2]Neurol., [3]Neurosurg., [4]Wu Tsai Inst., Yale Univ., New Haven, CT; [5]Princeton Neurosci. Inst., [6]Psychology, Princeton Univ., Princeton, NJ

Abstract: We often need to respond differently to similar experiences. The hippocampus supports this via pattern separation, orthogonalizing representations of similar experiences to reduce interference during retrieval. However, cortical contributions to this process remain underexplored, and it is unclear how the brain maintains similar memories over time after pattern separation. Using local field potentials from individuals with epilepsy implanted with chronic responsive neurostimulation (RNS) devices in bilateral hippocampus, we previously found that correctly distinguishing an experience from a similar memory drove repulsion of hippocampal representations beyond orthogonalization when they were later probed. However, these patients had hippocampal coverage only, leaving open the role of cortex in memory differentiation. Here we address this gap in 9 individuals with epilepsy who received acute intracranial EEG implants for seizure localization in both the hippocampus and cortex, allowing us to study the dynamics of how these systems interact. We additionally explore how differentiated memory representations change following offline sleep consolidation. Participants encoded a series of unique object images, then completed a memory test with encoded items (targets), highly similar objects (lures), and novel items (foils), labeling each as “old”, “similar”, or “new”. Finally, they were shown lures and their encoding counterparts immediately after the test (post-test 1) and after overnight sleep (post-test 2). Replicating our RNS finding, hippocampal representations of correctly identified lures reliably underwent repulsion (became anti-correlated) from similar encoding items 1.5-2 s after stimulus onset in post-test 1. To assess the role of cortex, ongoing analyses are comparing the timeseries of representational distinctiveness for similar image pairs across hippocampal and cortical electrodes using lagged cross-correlation. One possibility is that distinctiveness in visual cortex follows hippocampus in post-test 1, but this top-down modulation is reduced after sleep consolidation such that cortex can represent distinctiveness independently. Alternatively, visual cortex may lead hippocampus in post-test 1, as the unique perceptual features of similar lures may need to be represented in hippocampal input to trigger repulsion. The findings will clarify the complementary roles of hippocampus and cortex in resolving long-term memory competition.

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Nanosymposium

NANO36: Neural Representations Across Hippocampal Circuits and Memory Networks

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Presentation Number: NANO36.09

Topic: I.08. Learning and Memory

Support: Hewitt Foundation for Biomedical Research
NIMH R01MH128306

Title: Learning Compressed Representations for Memory Discrimination and Reward-Guided Choice

Authors: *D. ZHOU[1], S. GUO[1], S. M. NOH[2], N. HARHEN[3], N. V. BANAVAR[4], B. KIRWAN[5], C. A. HARTLEY[3], M. A. YASSA[1], A. M. BORNSTEIN[1];
[1]Univ. of California, Irvine, Irvine, CA; [2]Univ. of California Irvine, Irvine, CA, ; [3]New York Univ., Brooklyn, NY, ; [4]Univ. of California, Berkeley, Berkeley, CA; [5]Univ. of Pennsylvania, Provo, UT.

Abstract: A central challenge for memory processing is to efficiently structure experiences into useful representations. This is challenging when seemingly similar experiences require different responses or produce very different outcomes. In memory discrimination, this challenge is thought to be solved by expanding neural representations so that similar stimuli become maximally distinct. In reward-guided choice, it may require maintaining implausibly detailed memories of outcomes across many possible options. We propose that both abilities are aided by lossy compression, discarding redundant information while selectively retaining the task-relevant structure. First, we ask how memory discrimination can be supported by discarding redundant information from similar stimuli of everyday objects. We train neural networks to compress perceptual and semantic stimulus features and quantify lossiness using information-theoretic measures. Greater compressibility predicts memory discrimination on a mnemonic similarity task, particularly for higher-order visual representations extracted by convolutional networks. We replicate this finding across image sets, behavioral datasets, and measures of lossiness. Using fMRI, we identify replicable signatures of compression—dimensionality reduction and information loss—in V4, inferotemporal cortex, and hippocampal subregions DG/CA3 and CA1. Second, we ask whether compression restructures memory for reinforcement learning, where reward-maximizing behavior requires remembering an implausible amount of options and outcomes in naturalistic environments. Participants made sequential eat-or-leave decisions for 3,200 unique mushrooms in a *Super Mario* environment, learning latent reward structure through exploration. We quantified policy complexity—the mutual information between states and actions—as the representational cost of maintaining distinct choice rules. Critically, exploration drove progressive compression of policies and state representations over time, consistent with efficient coding of task-relevant structure. Individuals with more complex policies made more accurate and generalizable choices, earned greater reward, and selectively allocated information to stimulus dimensions governed by more complex reward functions. Together, these findings suggest compressed representations support memory discrimination and reward-guided choice.

Rather than preserving all available information, memory systems support decision-making by discarding redundant information while retaining dimensions most relevant for future decisions.

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Nanosymposium

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Topic: I.08. Learning and Memory

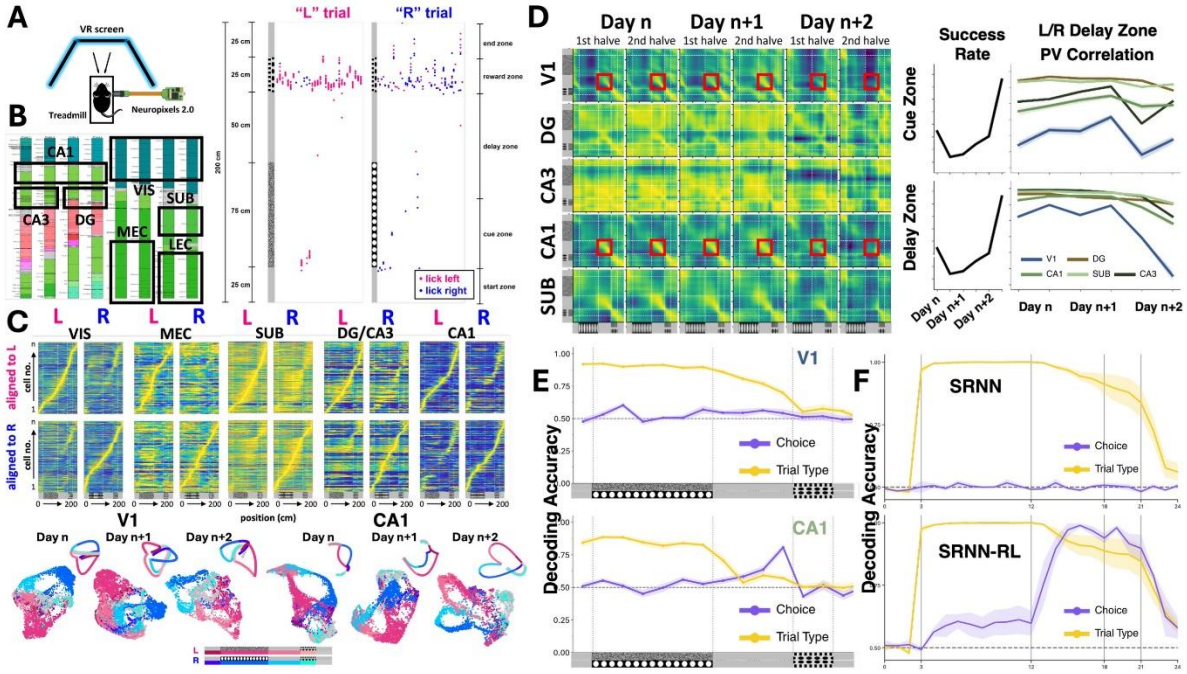
Support: IBMS of Academia Sinica

Title: Distributed Cortico-Hippocampal State Machines Support Parallel Representational Learning

Authors: *Y.-C. HUANG[1,3], C. YU[1,4], T.-H. LIU[1,5], C.-L. HSU[2,6,7];
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Abstract: The hippocampus has been considered a core substrate for cognitive map. However, where and how do such computations arise? Even large-scale CA1 recordings alone cannot address the problem regarding “map” generation within the hippocampus vs. through coordinated learning across brain circuits. To tackle this, we recorded simultaneously from visual, entorhinal, and hippocampal circuits in mice performing a memory-dependent two-alternative perceptual decision task in virtual reality (fig. 1a). Using dual multi-shank Neuropixels 2.0, we chronically tracked more than 450 neurons (fig. 1b) and analyzed representational geometry, decoding dynamics, information sharing, and millisecond-scale single-cell interactions over days. We found that state representations gradually emerged in both hippocampal and sensory cortical circuits (fig. 1c). Notably, the V1 exhibited a strong context-dependent code and developed splitter-like activity slightly earlier than the hippocampus (fig. 1d). We suspected primary sensory and higher-order regions encode distinct place information. In the delay zone, CA1 representations shifted progressively from encoding trial-type to behavioral choice (through virtual space), whereas V1 representations remained predominantly non-choice (fig. 1e). Millisecond-timescale information sharing was strong within hippocampal subregions but weak between hippocampus and V1. These observations motivated a computational model in which V1 acted as an unsupervised sensory-state learner, while the hippocampus implemented a behavior-guided state machine. They were modeled by spiking

recurrent neural networks (SRNNs) with Hebbian plasticity, or additionally augmented with Three-Factor-like learning, respectively. The model well recapitulated the empirically observed coding dynamics (fig. 1f). Together, we found a parallel cross-areal “map” learning beyond the hippocampal cognitive-map dogma.



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Title: Task-stage-specific modes of beta frequency coordination in the hippocampal-neocortical network

Authors: *P. TOPTAS, K. LEW, G. WANG, A. E. KAYE, Z. LEVERONI, J. PROCTOR-BONBRIGHT, U. MANI, J. GUTIERREZ, B. GARCIA CORADO, J. Y. YU;
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Abstract: Making decisions based on sensory information involves two critical processes: using sensory cues to select the next action and evaluating the outcomes of those actions. Although these processes unfold continuously in time, they are hypothesized to engage distinct computations. Beta oscillations in the hippocampal-neocortical networks are thought to support the distinct computations involved in both cue sampling and goal attainment. Yet how the dynamics of beta oscillations across distributed brain networks switch to support the computations required for each task stage remains poorly understood. During cue sampling, beta oscillations coordinate hippocampal-neocortical networks which is hypothesized to support the retrieval of sensory association memories for decision-making. During goal attainment, beta oscillations emerge in hippocampal-neocortical networks but appear not to be coordinated. These results suggest that the beta oscillations in the hippocampal-neocortical networks might function differently in different task stages. However, because prior work on beta dynamics investigated cue sampling or goal attainment using distinct behavioral paradigms (spatial navigation or operant conditioning), it remains unknown if the observed differences in beta dynamics stem from unique task paradigms or reflect genuine differences in network states between cue sampling and goal attainment. To address this question, we characterized beta-frequency activity in hippocampal-neocortical networks during cue sampling and goal attainment while rats performed an odor-guided two-alternative forced-choice (2AFC) task, allowing us to directly compare network dynamics associated with the two task stages within the same task and in the same animal. We found that these two stages showed unique patterns of beta-frequency power and coherence within the CA1-PFC network, including differences for subbands of beta. Furthermore, we found that ensemble spiking activity patterns in the CA1 and PFC differed between the two task stages and beta oscillations also showed task-stage-specific phase modulation of subsets of the CA1 and PFC populations. These results suggest that, even when compared in the same task paradigm, hippocampal-neocortical networks have distinct beta activity patterns during distinct task stages. Thus, task stage specific reconfiguration of these networks could support distinct computational requirements within a cognitive task.

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Title: Hippocampal Functional Connectivity Across Fetal and Neonatal Development

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Abstract: The hippocampus (HP) undergoes dramatic growth across fetal and neonatal periods. During this critical period, a variety of early environmental and clinical factors, including premature birth, have been shown to impact HP development. However, longitudinal patterns of HP functional connectivity in this period of dynamic development are still poorly understood. A detailed understanding of normative development is still needed to precisely understand the timing and progression of divergent HP growth in at-risk populations. In these analyses, we characterize connectivity patterns of the HP across fetal and neonatal periods. Resting state functional MRI data from healthy and preterm participants in the developing Human Connectome Project (dHCP; N=215 fetal, N=486 full-term, and N=216 preterm) were analyzed. Minimally preprocessed dHCP images were smoothed, bandpass filtered, and motion censored. The HP label from a fetal (CRL) and neonatal (UNC) atlas were divided into head, body, and tail subregions, and transformed into template space. Seed-based correlation analyses were performed, with a voxel-wise threshold of $p<0.001$ and cluster thresholds set based on permutation testing. Age, sex, and frames censored for motion were included as covariates. Both fetal and full-term groups showed strong connectivity in regions proximal to the HP, including parahippocampal gyrus and amygdala. Neonatal maps showed connections with additional regions seen in adult networks, including contralateral HP, bilateral motor, and parietal regions (Figure 1A). Both groups showed significant differences across longitudinal axis subregions (Figure 1B). Clusters of age-related increases and decreases in connectivity were seen in both groups. Compared to preterm participants at term equivalent age, full-term participants showed large regions of stronger HP connectivity (Figure 1C). Altogether, precursors of adult HP memory networks are present even in fetal periods and become increasingly adult-like by term equivalent age, with clear disruptions in this process due to prematurity.

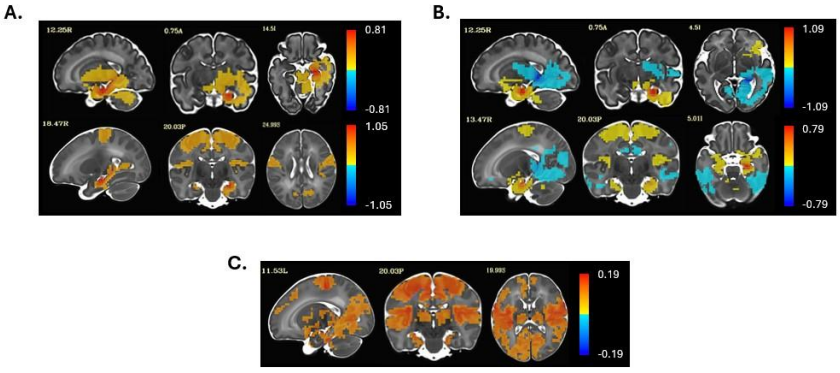


Figure 1. A) Fetal (top) and full-term neonatal (bottom) maps of the top 10% of connections from the right hippocampal seed. B) Differences between fetal (top) and full-term (bottom) connectivity maps between the right hippocampal head seed and the right hippocampal tail seed. C) Differences between connectivity maps from the right hippocampal seed in the full-term group compared to preterm participants at term-equivalent age.

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Title: Toward a Foundational Cell Type Atlas for a Human and Mammalian Brain Cell Atlas

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Abstract: The goal of the NIH BRAIN Initiative Cell Atlas Network (BICAN) is to generate a standardized, integrated cell atlas of the human, macaque, marmoset, and mouse brain that can serve as a foundational community reference for the classification and study of brain cell types. The initial stage of analysis and cell atlasing incorporated a joint anatomic sampling plan focused on creation of a cross-species, multimodal atlas of the basal ganglia, a set of subcortical nuclei central to motor control and implicated in a wide range of neurological disorders. The cell atlas is based on a transcriptomic classification of single cells that are integrated with epigenomic and spatial genomic mapping, supported by parallel sampling and harmonized analysis across species. It provides extensive phenotypic characterization of cell types, incorporates community-informed annotation, and establishes a highly curated, data-driven taxonomy with standardized nomenclature. The atlas is anchored to species-specific anatomical reference frameworks and connected across species through a harmonized ontology of the mammalian brain. Multiple complementary datasets are mapped to this reference, including multiomic profiles and developmental trajectories aligned to adult cell states. Realization of this resource has required coordinated standards for human and animal tissue processing, harmonized donor metadata

across brain banks, and unified anatomical reference systems. To enable these advances, BICAN has developed an integrated ecosystem of standardized sequencing pipelines, neuroanatomically grounded data infrastructure, scalable visualization and mapping tools, and interoperable metadata standards. Analogous to standardization achieved in genome sciences, these data resources, tools, and collaborative infrastructure form a FAIR (findable, accessible, interoperable, and reusable) framework that enables researchers to map, compare, and interpret diverse datasets against a shared reference and associated knowledge base. The BICAN reference system is now being extended to the whole brain, with principles that are readily generalizable to other organ systems.

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Title: Managing multi-modal data access in a distributed data ecosystem

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Abstract: The BRAIN Initiative Cell Atlas Network (BICAN: brain-bican.org) is a multi-institute consortium for brain cell-type classification and atlasing across multiple species and developmental stages. The BICAN Data Ecosystem includes specimen portals, data repositories, metadata catalogs, and standards that are integrated to ease access to diverse digital assets, supporting use and reuse across BICAN and the broader scientific community. A key value proposition offered by the BICAN is datasets generated using multi-modal techniques where individual specimens generate data from multiple modalities (multi-omics, imaging,

electrophysiology, behavioral data), and across levels from raw data outputs (sequence-level data, imaged tissue samples, voltage recordings) to complex processed data products (cell-type annotations, electrophysiological and morphological features). Ensuring findability and accessibility of linked data assets across portals and archives thus presents a key challenge for realizing the full value of BICAN datasets. BICAN has a state-of-the-art public database for sharing donor and tissue specimen provenance and metadata (NIMP Analytics: brain-specimenportal.org/nimp_analytics), and BICAN utilizes a consortium-wide identifier policy to facilitate linkage of data at BICAN repositories to specimens of interest for scientific users. We present efforts within BICAN led by our Metadata and Ontologies and Data Release working groups to manage data access using cross-pipeline integrated data models and cross-archive metadata schemas to facilitate specimen and data tracking across the full data ecosystem. As a use case for this integrated ecosystem we highlight the Patch-seq pipeline, a multi-modal assay that has been a cornerstone of both the BICAN and the preceding BICCN (BRAIN Initiative Cell Census Network), integrating transcriptomic, electrophysiological, and imaging data modalities from individual cells to enable multi-faceted cell type annotations. Each of these datatypes is handled by a separate BRAIN Initiative Archive: omics data at NeMO (nemoarchive.org), imaging at BIL (brainimagelibrary.org), and electrophysiology at DANDI (dandiarchive.org). We show how integrating metadata standards and employing common identifiers across archives enables effective data linkage at the level of both single cell specimens and complete datasets. With this approach, multi-modal raw and derived data can be connected through the Brain Knowledge Platform Data Catalog (knowledge.brain-map.org/data) and knowledge bases, enabling tracking of data provenance and data discovery across the BICAN ecosystem.

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Title: Age-related differences in transcriptional variability are brain region- and cell type-specific

Authors: *E. A. SMITH[1], K. WATKINS[1], W. YANG[3,5], A. DECASIEN[6], M. O'NEILL[4], M. O. BOHLEN[7], A. MELIN[8], J. HIGHAM[9], M. J. MONTAGUE[10], M. L. PLATT[11], J. SHENDURE[4], K. CHIOU[12], N. SNYDER-MACKLER[2];
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Abstract: Aging is associated with brain-wide molecular changes, and no two brains age the same way. Inter-individual differences in extrinsic factors, genetic background, and stochastic aging processes contribute to this heterogeneity, yet the molecular consequences across regions and cell types are poorly understood. Regions and cells with age-associated inter-individual variability differences may highlight biological processes contributing to divergent aging trajectories, while those with stable variability reflect conserved aging patterns. We examined age-related transcriptional differences in free-ranging rhesus macaques, whose genetic similarity to humans and age range that can be sampled in a naturalistic environment make them a valuable model to study human aging mechanisms. We drew on single-nucleus RNA sequencing of 5.3 million cells across 11 brain regions in 53 macaques (aged 3-21 years) to characterize age-related transcriptional variability at single-cell resolution. We tested for age differences in inter-individual variation in two ways: 1) cell compositions by quantifying beta diversity; and 2) cell-type-specific transcription by quantifying gene expression variance at the transcriptome-wide or gene level. Age was associated with region- and cell type- specific differences in compositional and transcriptional diversity. Hippocampal GABAergic neurons showed higher compositional diversity in older individuals ($q=0.031$). Transcriptional variability was higher at older ages in some cell subtypes, such as dlPFC myelinating oligodendrocytes ($q=0.013$) and lower in others, such as EC homeostatic astrocytes ($q=0.024$). We characterized the impact of this variability through functional enrichment and cell-cell communication assays and identified putative upstream regulators through gene regulatory networks (GRNs). We found mitochondrial function, cell signaling, and GRN signatures unique to subtypes that show variability differences with age. Some subtypes showed variability and signaling differences with age, including stronger signaling to oligodendrocyte precursor cells ($q<1e-20$, FE=6.2-28.4 in ACC, CN, IPP, M1, and dlPFC) and weaker signaling to oligodendrocytes ($q<1e-20$, FE=1.5-9.8 in CN, EC, HIP, IPP, M1, MB, NAc, dlPFC, and mdTN). By pinpointing regions, cell types, and genes vulnerable to greater variability and those stable with age in a human-relevant animal model, our work helps localize regulatory mechanisms that explain how brains age differently.

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Support: NIH BRAIN Initiative UM1MH130966

Title: Large-scale spatial transcriptomic characterization of adult human brain

Authors: *H. GAO[1], A. MOHSIN[1], S. BURGER[1], E. MURATOGLU[1], C. R. VANDERBURG[1], O. YOO[1], N. NAVARRO SUAREZ[1], N. BUDNIK[1], G. FISCHER[1], E. MACOSKO[1,2], K. ICHIHARA[1,3];
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Abstract: The human brain is a central target for biomedical research due to its complexity in cell types and cellular functions. Building on a foundational understanding of brain structure and function, advanced technologies developed in recent decades have created the ability to further investigate the human brain at cellular and subcellular levels. One challenge in spatial transcriptomics is achieving high-resolution spatial profiling across large, heterogeneous tissues, due to limitations in gene panel coverage and sample capture area. As part of the NIH BRAIN Initiative Cell Atlas Network (BICAN), we are working towards establishing a comprehensive cell atlas of a representative adult human brain hemisphere through high-volume whole transcriptome spatial mapping. Slide-tags, the recently developed sequencing-based spatial genomics technology, allows for spatial mapping at a significantly larger scale through integrating nuclei spatial barcoding and single-nucleus RNA sequencing (10x Genomics GEM-X 5' and NovaSeq X). Here, we report substantial improvements in the capture scale and performance of the Slide-tags platform, expanding its spatial coverage to approximately 40 cm^2. This advancement enables us to quantitatively examine the relative abundance of different cellular populations at single-cell resolution, across >30 coronal slabs from an entire postmortem human brain hemisphere. Our dataset identifies corresponding transcriptomic spatial patterns in both cerebral cortical layers and subcortical regions, such as the hippocampus, thalamus, amygdala, and the brainstem. This work provides a framework to identify important cell populations and serves as a transcriptomic baseline for studying their vulnerability to neuropsychiatric and neurological disorders.

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Topic: A.06. Developmental Disorders

Title: Single Cell Analysis Profiling Reveals Cell-Type-Specific Consequences of Rnu12 Dysfunction in Early-Onset Cerebellar Ataxia

Authors: *B. MANKALIYE[1,2], H. U. TILGNER[1], M. ROSS[2];
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Abstract: The minor spliceosome processes ~0.5% of introns yet regulates highly conserved genes essential for neurodevelopment. We identified a recessive 84C>T mutation in RNU12, encoding the U12 small nuclear RNA, as the cause of early-onset cerebellar ataxia (EOCA), characterized by cerebellar hypoplasia, progressive ataxia, and dysarthria. To define the cellular consequences of impaired minor splicing, we generated a knock-in mouse model carrying the patient-derived Rnu12 mutation and performed complementary short- and long-read single-cell RNA sequencing of postnatal cerebella.Cell-type-resolved analyses revealed widespread transcriptional and splicing abnormalities across cerebellar populations. Differential expression affected both minor intron-containing genes and key regulators of cerebellar development and function. Long-read sequencing identified extensive splice defects, including minor intron retention, exon skipping, and altered isoform usage, particularly among RNA-binding proteins and other post-transcriptional regulators. Granule cells exhibited especially prominent transcriptomic and isoform-level alterations.These findings demonstrate that Rnu12 dysfunction disrupts both gene-expression programs and transcript architecture in a cell-type-dependent manner, implicating defective RNA processing as a central driver of EOCA pathogenesis. More broadly, our results establish a framework for understanding how minor spliceosome dysfunction contributes to neurodevelopmental disease and highlight spliceosomopathies as an underexplored source of neurological disorders and potential therapeutic targets.

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Title: A spatial single-cell atlas of the claustro-insular region uncovers NR4A2 as a key regulator of neuronal identity and excitability

Authors: *L. FODOULIAN[1,2,3], M. BOILLAT[1,2], M. MOULINIER[1,3], A. CARLETON[3,1], I. RODRIGUEZ[2,1];
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Abstract: The claustro-insular region is a deeply interconnected and evolutionarily conserved brain structure implicated in attention, cognitive adaptability, interoceptive signaling, and emotional regulation. However, limited knowledge of its cellular organization has constrained understanding of the biological basis of these functions. Here, we combined single-cell RNA sequencing with spatial transcriptomics to map the mouse claustro-insular region at high resolution, identifying diverse neuronal populations and previously unrecognized cellular heterogeneity. Using this resource, we examined the contribution of NR4A2, a neuropsychiatric disease-associated factor expressed in multiple claustro-insular neuronal classes. Analysis of an *Nr4a2* haploinsufficient mouse model revealed selective alterations in transcriptional identity within claustrum neurons, while other neuronal populations remained largely unaffected. This identity shift, which involved the activation of a transcription factor cascade in which *Nr2f2* and *Cux1* played critical roles, was associated with altered neuronal firing activity. Guided by the single-cell transcriptomic data, we demonstrated that hypoexcitability of claustrum neurons was mediated by overexpression of the ryanodine receptor *Ryr2*, a key component of the calcium-induced calcium release mechanism. Transcriptomic and electrophysiological alterations were also accompanied by changes in claustro-insular cellular composition, predominantly affecting claustrum neurons. Our findings provide new insights into the cellular architecture of the claustro-insular region and highlight *Nr4a2* as a master regulator of its components' identities.

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

Support: KHIDI

Title: Methylation-Preserving DNA Amplification Enables Multi-Scale Epigenomic Analysis of Human Neurodevelopment, Disease, and Single Cells

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Abstract: DNA methylation is a fundamental regulator of cellular identity, development, and disease, yet comprehensive methylome analysis remains challenging in low-input samples such as cell-free DNA (cfDNA), rare cell populations, and single cells. Current approaches often rely on bisulfite conversion or enrichment strategies that can compromise DNA integrity, sensitivity, and downstream multi-omic integration. Here, we present a DNMT5-based methylation amplification platform that preserves methylation information while enabling sensitive epigenomic profiling from limited DNA inputs.Using synthetic DNA templates with defined methylation architectures, we demonstrate that DNMT5 faithfully amplifies complex methylation patterns while maintaining methylation-state fidelity. Application to low-input cfDNA samples improved recovery of biologically relevant methylation signatures while preserving methylation signal structure.To evaluate biological utility, we integrated DNMT5-derived methylome profiling with transcriptomic and isoform-level analyses in human induced pluripotent stem cell (iPSC) models of neurodevelopment and Fragile X syndrome. Across differentiation from pluripotent stem cells to neural progenitors and mature neurons, DNMT5-enabled profiling captured dynamic developmental methylation trajectories and revealed relationships between epigenetic remodeling, gene regulation, and transcript diversity. These findings demonstrate the utility of methylation-preserving amplification for studying developmental and disease-associated epigenetic programs.We further extended the platform to low-cell-input and single-cell applications using heterogeneous mixtures of BT474, HeLa, and HEK cells. DNMT5 amplification preserved cell-type-specific methylation signatures, enabled discrimination of mixed cellular populations, and maintained reproducible performance across decreasing cellular inputs.Together, these results establish DNMT5-mediated methylation amplification as a versatile platform for methylome analysis across development, neurological disease, liquid biopsy, and single-cell applications. By enabling robust epigenomic profiling from previously inaccessible samples, this approach provides a foundation for integrated multi-omic investigations of cellular identity, development, and disease.

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Title: Concordant transcriptional and morphological remodeling revealed by in vivo Perturb-CLEAR

Authors: *B. WU[1,2], S. K. SIMMONS[3], J. LI[1,2], M. A. AKRAM, Jr.[4], C. S. PARK[4], X. ZHENG[1,2], T. NYASULU[1,2], X. YANG[4], X. JIN[1,2];
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Abstract: The principle that form follows function has long guided thinking in biology and architecture alike. In the nervous system, however, form does more than reflect function: neuronal morphology actively constrains input patterns, synaptic integration, and circuit wiring. During postnatal neurodevelopment, dendritic architectures are assembled and remodeled through genetically encoded programs and activities, transforming molecular programs into circuit architecture. However, dendritic morphogenesis has been difficult to quantify at scale while systematically testing how genetic variants, including neurodevelopmental disorder (NDD) risk genes, alter these structures *in vivo*. We developed Perturb-CLEAR, which integrates pooled CRISPR screening and whole-mount imaging to quantify brain-wide cytoarchitecture, and paired it with Perturb-seq to link structural phenotypes to transcriptomic changes. Applying Perturb-CLEAR to the developing mouse cortex revealed morphogenesis trajectories accompanied by transcriptomic dynamics. Moreover, systematic perturbation of NDD risk genes uncovered gene-specific multimodal phenotypes. *Adnp* perturbation remodels basal dendrites in L4/5 IT (intratelencephalic) neurons but not other dendritic compartments or cell types, alongside

consistent transcriptional shifts. Combined morphology and transcriptome analyses link NDD risk genes to concordant multimodal cellular phenotypes in the developing brain, highlighting diverse paths of perturbation effect propagation across modalities.

Disclosures: B. Wu: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Scripps Research. **S.K. Simmons:** None. **J. Li:** None. **M.A. Akram:** None. **C.S. Park:** None. **X. Zheng:** None. **T. Nyasulu:** None. **X. Yang:** None. **X. Jin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Scripps Research.

Nanosymposium

NANO37: Single-Cell Analysis

Location: WCC Rm 145

Time: Tuesday, November 17, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO37.09

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

Support: NIH Grant U19NS130607

Title: A Deep Learning Framework Enables Transcriptomic Characterization from Neuronal Spike Waveform

Authors: *P. GUPTA[1], M. HOLMES[2,3], R. W. GEREAU, IV[4];
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Abstract: Recent advances in single-cell multimodal technologies have presented unique opportunities for measuring multiple characteristics of individual cells including transcriptomics, electrophysiology and morphology. Although many machine learning strategies have been developed that can be employed to integrate and analyze these multimodal datasets for deciphering correlations between transcriptomic characteristics with the electrophysiological features. However, these strategies rely on manually defined feature extraction from various data modalities or dimensionality reduction strategies which are susceptible to instability and poor generalization, especially with the electrophysiological datasets. Here, we demonstrate a deep learning framework that enables transcriptomic cell-type identification from electrophysiological recordings. We found that neuronal spike waveform is sufficient to enable cell-type identification with high accuracy (~95%), thereby alleviating the instability and poor generalization issues associated with previously developed machine learning strategies. The ensemble neural waveform trajectory analysis illustrated the unique upstroke and downstroke trajectory for distinct cell-types demonstrating the richness of information in the spike waveform which is not well realized by manually defined electrophysiological features. We have applied and benchmarked this proposed deep learning framework with two independent datasets

collected utilizing different techniques: (1) patch-seq technique and, (2) intracellular electrophysiology form genetically labelled neurons, further demonstrating the ubiquitous applicability of the proposed framework. We envision that such a strategy could be employed to develop a unified framework which can identify the cell-type from the intracellular recordings obtained from unlabeled cells which remain elusive.

Disclosures: P. Gupta: None. **M. Holmes:** None. **R.W. Gereau:** None.

Nanosymposium

NANO37: Single-Cell Analysis

Location: WCC Rm 145

Time: Tuesday, November 17, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO37.10

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

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University of Virginia Grant: Brain Institute - Presidential Fellowship in Collaborative Neuroscience
NIH Grant R01 NS083378
NIH Grant R01 NS136342
NIH Grant R01 NS111220

Title: A Single-Cell Signaling Atlas of Spinal Cord BDNF Responses Reveals Determinants Beyond Receptor Expression

Authors: *J. SEWELL[1], E. ZUNDER[2], B. R. WINCKLER[3], C. DEPPMANN[1];
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Abstract: During periods of change, nervous system cells must rapidly decode extracellular cues to enact processes like differentiation, synaptic remodeling, or damage mitigation. While such responses are well-characterized by aggregate bulk phosphorylation or single-cell transcriptomics, an understanding of multi-pathway phosphoprotein heterogeneity across distinct cell populations is lacking. To address this gap, we utilized highly multiplexed single-cell mass cytometry (CyTOF) to simultaneously measure 19 signaling markers and 18 cell identity markers across primary embryonic rat spinal cord cultures. As a biological validation of this platform, we treated cultures with Brain-Derived Neurotrophic Factor (BDNF) and constructed a high-resolution temporal atlas of induced signaling (5 minutes to 16 hours) relative to control conditions across diverse spinal lineages and maturation states.
Initial aggregated pseudobulk analysis recapitulated canonical Ras/MAPK and PI3K/Akt activation, but single-cell resolution revealed masked heterogeneity: only a discrete subpopulation (47-75%) of cells responded at peak activation, highlighting the limitations of aggregate methods. Leiden clustering partitioned cells into 20 unique populations, resolving

neurons along a developmental trajectory and distinct glial subtypes. While astrocytes and mature NeuN-high neurons responded robustly, Sox2+ neural progenitors and unladen microglia remained largely signaling-silent despite harboring high total receptor levels. This paradox correlated with surface receptor dynamics: responsive cell types exhibited significant ligand-induced surface TrkB depletion, whereas unresponsive progenitors maintained stable surface levels, suggesting a trafficking-based signaling block. Strikingly, isolating subpopulations matched for identical surface levels of the BDNF receptors TrkB and p75NTR still yielded fundamentally divergent signaling patterns across cell types, suggesting that cell-intrinsic identity acts as the final arbiter of the BDNF message.
These findings reframe BDNF sensitivity as a form of prepared competence dictated by internal cellular machinery rather than simple receptor density. More broadly, this work benchmarks CyTOF as a high-throughput pipeline to resolve complex signaling topography in neural systems. This scalable framework can readily be applied to diverse stimuli beyond growth factors to investigate questions from therapeutic drug mechanisms to intercellular communication via extracellular vesicles.

Disclosures: J. Sewell: None. **E. Zunder:** None. **B.R. Winckler:** None. **C. Deppmann:** None.

Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

Location: WCC Rm 145

Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.01

Topic: B.04. Synaptic Transmission

Support: Technology Agency of the Czech Republic (TA CR), Grant TN02000109

Title: Steroidal modulators of NMDA receptors enhance presynaptic glutamate release and increase locomotor activity in zebrafish larvae despite opposing postsynaptic effects

Authors: *M. KURUC[1,2], M. KORINEK[2], V. ABRAMOVA[2], L. VYKLICKY[2];
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Abstract: Neurosteroids have emerged as potent endogenous and synthetic modulators of NMDA receptors (NMDARs), producing either inhibitory or potentiating effects. Despite detailed molecular insight, the behavioral consequences of neurosteroid modulation remain poorly understood. This study aimed to link the molecular pharmacology of neurosteroids to their behavioral effects. Using whole-cell patch-clamp electrophysiology, we examined neurosteroid actions on recombinant rat (GluN1-1a/GluN2A, GluN1-1a/GluN2B) and zebrafish (GluN1a/GluN2Aa, GluN1a/GluN2Bb) NMDARs expressed in HEK293 cells and on synaptic transmission in rat hippocampal autaptic cultures. Behavioral effects were assessed by measuring spontaneous locomotor activity in zebrafish larvae ($n \approx 20$ per concentration) following a 1-h preincubation with the compounds.

In vivo, ketamine (30-300 μM), used as a reference NMDAR antagonist, significantly reduced locomotor activity versus control ($p < 0.001$). In contrast, the steroidal NMDAR inhibitors pregnanolone sulphate (3-30 μM) and 17-ethyl-androstane sulphate (17Et-AND-S; 1-10 μM) significantly increased locomotor activity ($p < 0.001$). The steroidal positive allosteric modulators pregnenolone sulphate (30-300 μM) and 4-(20-oxo-5β-pregnan-3β-yl)butanoic acid (EPA-But; 0.1-3 μM) similarly increased locomotor activity ($p < 0.001$). At the cellular level, 17Et-AND-S inhibited recombinant NMDARs with similar potency at rat and zebrafish receptor subtypes (IC_{50} = 0.58-0.91 μM), validating the zebrafish model. In autaptic neurons, 10 μM 17Et-AND-S increased AMPAR-mediated eEPSC amplitude by 41 ± 5% and decreased paired-pulse ratio by 34 ± 7% ($n = 8$, $p < 0.001$), indicating enhanced presynaptic glutamate release. AMPA-evoked currents were unchanged by 10 μM 17Et-AND-S ($n = 6$), excluding postsynaptic AMPAR modulation. EPA-But potentiated recombinant NMDAR responses in both rat and zebrafish receptors at 3 and 10 μM. In autaptic neurons, 15 μM EPA-But increased AMPAR-mediated eEPSCs by 65 ± 9% and decreased paired-pulse ratio by 22 ± 5% ($n = 9$, $p < 0.001$), again indicating enhanced presynaptic glutamate release. AMPA-evoked currents were unchanged by 15 μM EPA-But ($n = 6$).
Both negative and positive steroidal modulators of NMDARs increased locomotor activity despite producing opposite effects on receptor function. We suggest that this convergence may be related to the shared presynaptic facilitation of glutamate release. In contrast, their opposing postsynaptic effects at NMDARs appear to play a less prominent role. These findings have implications for the development of neurosteroid-based therapies targeting NMDAR dysfunction.

Disclosures: M. Kuruc: None. **M. Korinek:** None. **V. Abramova:** None. **L. Vyklicky:** None.

Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

Location: WCC Rm 145

Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.02

Topic: B.04. Synaptic Transmission

Support: R01MH136706

Title: Two Fuels, One Synapse: Demand-Dependent Metabolic Specialization Governs Vesicle Recycling and Transmission Fidelity in Human Stem Cell-Derived Neurons

Authors: *V. ARORA[1], D. FREDERICK[2], S. A. ANDERSON[3,4], A. ROSSANO[2,4];
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Abstract: Synaptic vesicle cycling and glutamate release impose intense adenosine triphosphate (ATP) demands on presynaptic terminals, yet whether glycolysis and oxidative phosphorylation

(OXPHOS) serve non-redundant, state-dependent roles at human synapses remains poorly understood. This question has direct relevance to 22q11.2 deletion syndrome, where impaired mitochondrial function is proposed to impair glutamatergic transmission and contribute to neuropsychiatric vulnerability. Human embryonic stem cell (hESC)-derived excitatory neurons (iNeurons; NGN2-inducible, 22q11.2 deleted and isogenic control line) were cultured with rat astrocytes. Approximately 70% of iNeurons expressed a vGlut1-pHluorin/Scarlet reporter of synaptic vesicle cycling and ~30% expressed iGluSnFR3, a postsynaptic glutamate sensor. Release probability (Pr) was assessed by field depolarization (30 pulses, 0.33 Hz) across extracellular Ca^{2+} concentrations (0.5-4 mM) in the presence of glutamate receptor blockers. Glycolysis was inhibited with 2.5 mM 2-deoxyglucose (2-DG), OXPHOS with rotenone (5 µM), and combined blockade with 2-DG + rotenone. Vesicle dynamics were evaluated using high-frequency stimulation (HFS; 300 pulses, 5 Hz) followed by recovery testing. Rotenone reduced evoked glutamate responses consistent with lowered Pr but preserved HFS-driven recovery, suggesting OXPHOS is not rate-limiting for vesicle recycling under moderate demand. In contrast, 2-DG (20 min, 4 mM Ca^{2+}, + pyruvate) caused near-complete loss of evoked transmission and abolished post-HFS recovery. The absence of fast release and HFS-driven vesicle recruitment implicates defects in vesicle filling, priming, and/or docking, demonstrating that glycolytic ATP is required to maintain releasable vesicle pools rather than support exocytosis. Under 2-DG, vGlut1-pHluorin fluorescence increased uniformly independent of stimulation, suggesting glycolysis is required to maintain synaptic vesicle acidification. Combined 2-DG + rotenone abolished evoked transmission and elevated baseline iGluSnFR3 fluorescence, indicating presynaptic failure and impaired astrocytic glutamate clearance. These findings reveal demand-dependent metabolic partitioning at human synapses: OXPHOS supports basal release, whereas glycolysis is essential for activity-dependent vesicle recycling and recovery following intense stimulation. The isogenic control line data establish a metabolic baseline for direct comparison with the paired 22q11.2-deleted line to determine whether 22q11.2 haploinsufficiency alters glycolytic/OXPHOS dependence and compromises synaptic function.

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Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

Location: WCC Rm 145

Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.03

Topic: B.04. Synaptic Transmission

Title: Regulation of inhibitory synapse development by synapse-enriched long non-coding RNA.

Authors: *K. GARG[1], B. SRINIVASAN[1], S. SAMADDAR[1], K. TOPPALDODDI[2], S. JANA[2], S. BANERJEE[1];
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Abstract: The regulatory role of non-coding RNAs in excitatory synapse development is well recognized; however, their involvement in inhibitory synapses formation remains largely unexplored. Through this study, we identified a previously uncharacterized long non-coding RNA (lncRNA), 2900052N01Rik (N01Rik), that specifically regulates inhibitory synapse development in the mouse hippocampus. Transcriptomic analyses performed previously in our laboratory identified synaptically enriched lncRNAs in hippocampal synaptic fractions. Developmental profiling during the window of synaptogenesis revealed the temporally regulated increase in the expression of several synaptically localized lncRNAs, indicating a prospective functional role in synapse formation. Among these, N01Rik exhibited peak expression between postnatal day (P7) to (P21), coinciding with critical period of synapse development and thereby qualifying it for further investigation. To investigate the functional significance of N01Rik, shRNA-mediated knockdown was performed in CA1 pyramidal neurons using *in utero* electroporation prior to synaptogenesis. Morphological and functional analyses revealed that N01Rik depletion selectively impaired inhibitory synapse development without affecting excitatory synapses. Specifically, N01Rik knockdown significantly reduced both perisomatic and dendritic inhibitory synaptic puncta. Electrophysiological recordings from primary hippocampal neurons demonstrated a significant reduction in miniature inhibitory postsynaptic current (mIPSC) amplitude, while mIPSC frequency remained unchanged, suggesting a postsynaptic deficit in inhibitory synaptic function. In contrast, miniature excitatory postsynaptic currents (mEPSCs) were unaffected. Transcriptomic analysis following N01Rik knockdown identified 206 downregulated transcripts enriched for cilia-associated biological processes, including cilium movement and motile cilium organization. Consistent with these findings, a reduction in ciliary abundance was observed in hippocampal CA1 neurons following N01Rik depletion. Furthermore, knockdown of a ciliary protein identified from the transcriptomic dataset recapitulated the decrease in mIPSC amplitude observed upon N01Rik loss. Together, these findings uncover a previously uncharacterized role for N01Rik in inhibitory synapse development and suggest that lncRNA-mediated regulation of cilia-associated pathways contributes to the establishment and function of inhibitory synaptic connectivity in the hippocampus.

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Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

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Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.04

Topic: B.04. Synaptic Transmission

Support: The Research Council of Norway
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UiO LifeScience

Title: Dietary Omega-3 Fatty Acids Selectively Enhance Synaptic Structure and Function in Hippocampal CA1 Stratum Oriens

Authors: *D. SARAJ[1], P. TERROBA NAVAJAS[5], M. WEHBE[2], E. J. MORLEY[6,2], H. RINGSEVJEN[2], T. EID[7], K. RETTERSTØL[1], S. HUSSAIN[3], S. DAVANGER[4];
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Abstract: Dietary omega-3 fatty acids influence hippocampal synaptic plasticity, but the underlying cellular and circuit-level mechanisms remain poorly understood. We previously demonstrated that dietary DHA/EPA selectively enhance long-term potentiation (LTP) in CA1 stratum oriens, but not stratum radiatum (Aryal et al., 2019). Here, we investigated the molecular, structural, and behavioral correlates of this layer-specific plasticity using Western blotting, immunogold electron microscopy, Golgi staining, and Morris Water Maze testing in young adult mice maintained on omega-3-enriched or omega-3-deficient diets.
Western blot analyses demonstrated increased hippocampal expression of the AMPA receptor subunits GluA1 and GluA2 and the NMDA receptor subunit GluN2B in omega-3 supplemented animals. These receptor subunits are critically involved in excitatory synaptic transmission and long-term potentiation. Immunogold electron microscopy further revealed significantly enhanced synaptic localization of GluA2-containing AMPA receptors in stratum oriens, whereas no significant effect was observed in stratum radiatum. Consistent with these molecular findings, Golgi analyses revealed a ~65% increase in filopodia density in stratum oriens, whereas no significant changes were detected in stratum radiatum across any spine subtype or morphological measure. These structural observations provide a potential anatomical substrate for the previously observed enhancement of oriens LTP. Conventional Morris Water Maze measures were largely unchanged, although omega-3 supplemented animals exhibited greater precision in locating the former platform position during probe trial.
Together, these findings identify a convergent molecular, structural and functional signature of omega-3-dependent plasticity in CA1 stratum oriens. Increased glutamate receptor expression, enhanced synaptic GluA2 localization, elevated filopodia density, and previously reported oriens-specific LTP enhancement converge to suggest that dietary omega-3 fatty acids selectively modulate plasticity within distinct hippocampal microcircuits. The accompanying improvement in spatial-memory precision further suggests that oriens circuitry may contribute to aspects of memory retrieval not captured by conventional Morris Water Maze measures.

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Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

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Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.05

Topic: B.04. Synaptic Transmission

Support: Gordon and Betty Moore Foundation 12263

Title: Axonal all-optical electrophysiology in behaving mice

Authors: *J. XU[1,2], X. WU[1,2], B. LEE[1,2], Y. WANG[1,2], Y.-C. HUANG[1,2], A. E. COHEN[1,2];
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Abstract: Axons transmit neuronal information through action potential firing. *In vitro* studies suggest that axons are not merely passive cables, but can actively modulate spike waveforms in complex ways that regulate neurotransmitter release. However, voltage dynamics in individual axons have not been mapped in the brains of behaving mice, largely due to the lack of suitable tools. Here, we developed molecular and optical approaches for axonal voltage imaging *in vivo*. We combined voltage imaging with local optogenetic stimulation and with calcium or glutamate imaging to investigate the mechanisms and functional consequences of axonal voltage dynamics. We mapped the voltage dynamics of thalamocortical axons in layer 1 of the somatosensory cortex during air-puff or optogenetic stimulation in awake mice. Both stimulus protocols revealed activity-dependent modulation of axonal spike waveforms and subthreshold dynamics over an integration window of several seconds. We then combined axonal voltage imaging with glutamate imaging to investigate how changes in spike waveform regulate downstream neurotransmitter release. Together, these tools establish a framework for mapping axonal function *in vivo* and reveal principles of axonal information processing in behaving mice.

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

Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

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Title: Organization of N-Methyl-D-Aspartate Receptors in the Postsynaptic Density of Excitatory Synapses

Authors: *X. CHEN[1,2], S. INCONTRO[4], C. A. WINTERS[2], M. ARONOVA[5], S. MOREIRA[3], R. D. LEAPMAN[6], R. A. NICOLL[7], T. S. REESE[2];

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Abstract: N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are the two primary types of ionotropic glutamate receptors embedded in the membrane of excitatory postsynaptic density (PSD). They are responsible for virtually all synaptic transmission and signal transduction events at excitatory synapses. NMDARs function as coincident detectors, enabling calcium influx that initiates cascades of events crucial for synaptic plasticity, including long-term potentiation (LTP) and depression (LTD). Conversely, AMPARs are responsible for most of the charge transfer at resting membrane potential, and the modulation of their numbers within the PSD are believed to be the essential element for the development and maintenance of LTP and LTD.To enable positive identification of NMDAR complexes in the intact PSD in hippocampal synapses, we applied a CRISPR-Cas9 Lenti viral construct to knockout the obligatory GluN1 subunit for the assembly of NMDARs, thereby eliminating NMDARs in neurons. Electrophysiology measurements demonstrate that over 12-16 days in vitro following the GluN1 knockout, NMDAR-mediated EPSCs are essentially eliminated, while AMPAR-mediated EPSCs increase significantly.Using dark-field scanning transmission electron microscopy (STEM) tomography, we compared the detailed ultrastructural changes of key elements within the core structure of the PSD under control and knockout conditions. Rat hippocampal cultures were high pressure frozen and freeze substituted. Sections 160-400 nm thick were imaged by dark-field STEM tomography, which significantly improved the signal-to-noise ratio compared with either TEM tomography or bright-field STEM tomography. We showed that transmembrane structures with bulky cytoplasmic aspects correspond to NMDARs, while those with thinner, flat cytoplasmic aspects correspond to AMPARs. NMDARs are often clustered in central region of the PSD. The elimination of NMDARs results in substantial reorganization of core elements within the PSDs; in particular, a notable increase in AMPAR type of structures and core scaffolding structures in PSD membrane. Our work combining dark field STEM tomography with CRISPR knockout presents the potential to monitor alterations in the macromolecular organization of PSDs at the level of individual glutamate receptors, information needed for interpreting synaptic plasticity at the molecular level.

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Nanosymposium

NANO38: Pre- and Postsynaptic Modulation

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Time: Wednesday, November 18, 2026, 8:00 AM - 9:45 AM

Presentation Number: NANO38.07

Topic: B.04. Synaptic Transmission

Support: ERC Advanced Grant 885069
Wellcome Discovery Grant 302077/Z/23/Z

Title: Spatial organisation of synapse protein lifetime across dendritic compartments and neuron types

Authors: *V. SAVOLAINEN[1,2], E. BULOVAITE[3], K. YUAN[3], D. DOMINIC[3], N. H. KOMIYAMA[2,3], S. G. N. GRANT[3,2];
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Abstract: Excitatory synapses exhibit widely differing rates of protein turnover, forming an organised brain-wide architecture that changes with disease-associated mutations and age. Synapses with long and short protein lifetimes have important implications for plasticity, memory persistence, and vulnerability to brain diseases, but it is not known how the diversity of synapse protein turnover rates manifests within the dendritic compartments of individual neurons in the intact brain, or how it differs between neuron types. To address this, we engineered mice to express HaloTags fused to endogenous synaptic proteins in response to Cre recombination, and labelled synapses and dendritic morphology in neuron subpopulations using Cre-expressing AAVs. We visualise protein turnover in individual neurons at single-synapse resolution via systemic pulse-chase delivery of HaloTag ligands. Using in-house built machine-learning-based 3D synapse segmentation, dendrite extraction, and spatial analyses, we map turnover features of functionally important endogenous synaptic proteins of different protein classes onto the dendritic architecture of neurons. To test for repeating spatial patterns of synapses with different morphological and protein turnover features along dendrites, we apply a new computational approach for “spatial sequencing” of synapse types. In cortical inhibitory neurons, the postsynaptic density protein 93 (PSD93) shows a somato-dendritic turnover rate gradient, with faster turnover at proximal synapses and slower turnover distally. Comparing inhibitory neurons with layer 5 extratelencephalic neurons reveals distinct turnover patterns, including differences in neighbour-to-neighbour variability in synapse protein turnover across the cell types ($n \geq 10$ cells; 5 mice per cell type; 4 female; 5 months old). Spatial sequencing of different synapse types along dendrites suggest the presence of recurring synapse type motifs expressed above the level of chance, with some types preferentially clustering together. Ongoing work extends these analyses to glutamate receptor 1 (GluR1) and calcium/calmodulin-dependent protein kinase II alpha (CaMKIIα) to test whether spatial turnover organisation is shared across protein classes or reflects protein-specific programmes. Together, these results reveal that synaptic protein turnover is spatially structured within dendritic trees and differs systematically between neuron types. This framework can be used to relate distinct proteostatic programmes to the plasticity profiles, computational features, and selective vulnerabilities of dendritic compartments and neuron types.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

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Presentation Number: NANO39.01

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

Support: NIH Grant R01 GM134327
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Title: Dissecting the role of Tmp21 in lysosomal function, dysfunction and amyloid beta accumulation

Authors: *A. GRANINGER[1], P. KRISHNAN[2];
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Abstract: Alzheimer's disease (AD) is a complex disorder. A large body of work has demonstrated that in AD, amyloid beta (Aβ), a toxic proteolytic product of amyloid precursor protein (APP), forms plaques in brain tissue. Additionally, evidence has accumulated for lysosomal and autophagosomal defects in the neurons of Alzheimer's brain tissue (1). Crucial insight has come from several recent publications demonstrating that AD patient brain tissue has reduced levels of TMP21 protein expression (2,3,4). However, the mechanism underlying TMP21 and AD is unclear. We engineered a TMP21-conditional knockout (cKO) system in HeLa cells, and investigated the relationship between TMP21 and Aβ. First, we discovered a robust phenotype in which Aβ stained brightly inside of the TMP21-depleted cells. Next, through colocalization analysis we identified the subcellular compartment containing the Aβ to be lysosomes. Furthermore, we observed that the lysosomes were swollen and perinuclear in TMP21-depleted cells, suggesting a defect in lysosomal degradation. To test this, we performed two fluorescence-based live cell imaging-based assays that provided a measurable readout of the degradative capacity of lysosomes. Intriguingly, we discovered that the lysosomes in the TMP21-depleted cells have markedly reduced capacity to degrade the substrates. Furthermore, we discovered a buildup of endosomal and autophagic markers that did not colocalize with lysosomes, suggesting that the lysosomes may harbor a fusion defect. We are currently performing live-cell imaging experiments to further assess this fusion defect. Our results suggest that TMP21 plays an underappreciated role in lysosomal function. We are using our TMP21 cKO cells to determine how TMP21 expression supports lysosomal function and regulates APP proteolytic processing in lysosomes, and the interrelationship between these two functions. We have developed an iPSC-derived neuron system to control TMP21 expression and test whether neurons present the same lysosomal phenotype as HeLa cells upon TMP21-depletion.Select references: 1. Lee, JH., et al. Faulty autolysosome acidification in Alzheimer's disease⋯ Nat Neurosci 25, 688-701 (2022) 2. Johnson ECB, et al. Large-scale proteomic analysis of Alzheimer's disease⋯Nat Med. 2020 May;26(5):769-780 3.Vetrivel KS. et al. (2008) Localization and regional distribution of p23/TMP21⋯Neurobio Dis. 32(1): 37-49. 4. Chen F. et al. (2006) TMP21 is a presenilin complex component⋯. Nature 440, 1208-1212.

Disclosures: A. Graninger: None. **P. Krishnan:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.02

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

Support: NIA5R01AG080984

Title: Neuronal and Microglial Lipid Droplet Accumulation is Differentially Altered in Response to Amyloid Pathology in the 5xFAD and AppNL-G-F Mice Models

Authors: *J. M. NOUGAISSE[1], Y. LEI[2], X.-Y. LU[2];
[1]Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA; [2]Neurosci. & Regenerative Med., Med. Col. of Georgia At Augusta Univ., Augusta, GA

Abstract: Altered lipid metabolism contributes to cellular dysfunction during aging and Alzheimer's Disease (AD). Lipid droplets (LDs) are dynamic organelles that regulate intracellular lipid storage and metabolism, and their accumulation in microglia has emerged as a feature of aged and AD brains. While aging, the primary risk factor for AD, is associated with neuronal LD accumulation, it remains unclear whether amyloid pathology further exacerbates neuronal LD accumulation. To address this question, we used BODIPY-based neutral lipid staining and confocal microscopy to characterize neuronal and microglial lipid accumulation in the hippocampus of two widely used amyloid mouse models, 5xFAD and AppNL-G-F. Mice of both sexes were included in experiments, and sex differences were analyzed when applicable. We found that in both 8-9-month-old 5xFAD mice and 26-27-month-old AppNL-G-F mice, microglial LDs were increased, whereas neuronal LDs are unexpectedly reduced even after accounting for neuronal cell loss. These findings reveal that amyloid pathology is associated with divergent LD responses in neurons and microglia, suggesting cell type-specific alterations in lipid metabolism during AD progression.

Disclosures: J.M. Nougaisse: None. **Y. Lei:** None. **X. Lu:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.03

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

Support: AMED JP24wm0625001
JSPS 26K02333

Title: Identification of seed-competent high-molecular-weight amyloid-beta species and their neutralization by mAb158

Authors: ***T. HASHIMOTO**[1], H. UCHIGAMI[1], M. KASHIWAGI-HAKOZAKI[2], Y. HORI[3], L. SÖDERBERG[4], C. MÖLLER[4], T. IWATSUBO[1];
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Abstract: The progressive deposition and propagation of amyloid-beta peptide Abeta pathology throughout the brain is a central pathogenic process in Alzheimer's disease and a major therapeutic target. However, the endogenous Abeta species that act as seeds to drive Abeta deposition and propagation remain poorly defined. Here, we found that Abeta seeding activity is present in the TBS-soluble fraction of brain lysate from plaque-bearing APP transgenic (tg) mice. Further fractionation by size-exclusion chromatography demonstrated that the activity was associated with Abeta species of > 150 kDa, hereafter referred to as peak 1 Abeta. Peak 1 Abeta contained Abeta oligomers, and inoculation of approximately 100 pM peak 1 Abeta into the hippocampus of young APP tg mice induced robust Abeta deposition. The seeding activity was abolished by denaturation with 70% formic acid, suggesting that Abeta oligomers present in the peak 1 Abeta fraction may represent the seed-competent species. We next investigated whether peak 1 Abeta corresponds to Abeta protofibrils, based on its solubility in TBS and its apparent molecular size. Consistent with this possibility, mAb158, the murine precursor antibody to lecanemab that selectively recognized Abeta protofibrils, bound peak 1 Abeta in both sandwich ELISA and dot blot assays. Importantly, immunodepletion of peak 1 Abeta with either anti-Abeta antibodies or mAb158 abolished its ability to induce Abeta deposition following hippocampal inoculation into young APP tg mice, indicating that mAb158 effectively neutralizes the seed-competent Abeta species present in the peak 1 Abeta. In contrast, inoculation of approximately 22 microM synthetic Abeta1-42 protofibrils into young APP tg mice failed to induce the robust Abeta deposition observed with peak 1 Abeta, suggesting that the seed-competent Abeta species present in peak 1 Abeta are not simply equivalent to synthetic Abeta protofibrils. Collectively, these findings identify peak 1 Abeta as a native seed-competent Abeta species in the brain and demonstrate that its seeding activity can be neutralized by mAb158, suggesting a potential mechanism by which lecanemab may neutralize pathogenic Abeta seeds and thereby interfere with the propagation of Abeta pathology.

Disclosures: T. Hashimoto: None. **H. Uchigami:** None. **M. Kashiwagi-Hakozaki:** None. **Y. Hori:** None. **L. Söderberg:** A. Employment/Salary (full or part-time):; BioArctic AB. **C. Möller:** A. Employment/Salary (full or part-time):; BioArctic AB. **T. Iwatsubo:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.04

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

Support: This study is supported by a start-up fund from the Department of Biology at Syracuse University

Title: Lysosome-acidifying nanoparticles restore lysosomal acidification and mitigate Aβ42 oligomer-induced neurotoxicity in cellular and mouse models of Alzheimer's disease

Authors: *K. A.-E. ABD-ELRAOUF[1], J. ZENG[2], C. LO[1];
[1]Biol., [2]Syracuse Univ., Syracuse, NY

Abstract: Abstract: Lysosomal dysfunction is an early and central event in Alzheimer's disease (AD), which is characterized by the accumulation of amyloid-β oligomers (AβO) that disrupt lysosomal acidification and autophagic flux. AβO has been shown to associate with lysosomal V-ATPase subunits, suggesting that its accumulation may disrupt proton pump function and further compromise lysosomal integrity. Whether restoring lysosomal acidification is sufficient to reverse the AβO-induced pathology remains unclear. Here, we tested the hypothesis that AβO impair neuronal function through lysosomal de-acidification and autophagy and mitochondrial dysfunction, and that lysosomal re-acidification can rescue these deficits. In SH-SY5Y neurons, AβO exposure induced lysosomal alkalinization, reduced cathepsin activity, and impaired autophagic flux, accompanied by decreased cell viability. These lysosomal defects were associated with mitochondrial fragmentation, increased reactive oxygen species, and reduced mitochondrial membrane potential, indicating downstream metabolic stress. Treatment with lysosomal acidifying nanoparticles (AcNPs) restored lysosomal pH, rescued cathepsin activity, and improved autophagic flux. AcNPs also improved mitochondrial function, leading to increased neuronal survival. Using APP^{NL-G-F} knock-in mouse model, we performed longitudinal analyses at 2, 4, 6, and 8 months of age to characterize progressive lysosomal dysfunction. Progressive disease was associated with reduced expression of V-ATPase subunits (including ATP6V1A, ATP6V1H, and ATP6V1C1) and increased p62 accumulation, consistent with impaired lysosomal acidification and autophagy failure. These changes correlated with age-dependent deficits in spatial memory, without significant locomotor impairment. Hippocampal administration of AcNPs improved autophagic functions and significantly rescued spatial memory performance. Collectively, these results establish lysosomal acidification failure as a potential driver of AβO-induced neurotoxicity and demonstrate that restoring lysosomal pH is sufficient to reverse downstream autophagy, mitochondrial, and cognitive deficits. Lysosome-targeted acidifying nanotherapeutics therefore represent a promising strategy for restoring cellular homeostasis in AD.

Disclosures: K.A. Abd-ElRaouf: None. **J. Zeng:** None. **C. Lo:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.05

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

Support: Cure Alzheimer's Fund

Title: Aβ Induces Endolysosomal Dysfunction via Rab GTPase Activation and Membrane Disruption

Authors: *U. DAS[1], D. MILLER[2], S. VOLPI[2], X. ZUO[3], X.-Q. CHEN[4], A. BECKER[2], W. C. MOBLEY[5];
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Abstract: Background: In Alzheimer's disease (AD), hallmark features include extracellular amyloid beta (Aβ) plaques and intracellular tau tangles. Although therapies targeting extracellular Aβ pathology have shown promise in animal models, clinical trials in AD patients have largely failed to demonstrate efficacy. This discrepancy may stem from Aβ pathology being a late manifestation of the disease, underscoring the need to investigate earlier pathogenic pathways. To identify earlier pathogenic mechanisms, we investigated endolysosomal dysfunction in AD and DS-AD models. Emerging evidence, including GWAS data, implicates the endolysosomal network (ELN) as a central hub in the initiation of AD and DS-AD; however, the mechanistic link between ELN dysregulation and disease onset remains unresolved. Methods: We employed cellular models of Aβ-induced ELN dysregulation to examine endolysosomal membrane-associated Rab GTPases using biochemical and imaging analyses. These studies were further extended to human iPSC-derived neurons representing sporadic and familial forms of AD, as well as DS-AD. Results: Endocytosed Aβ trafficked from early to late endosomes/lysosomes, causing accumulation of Aβ and APP-CTFs within the ELN. This buildup resulted in Rab5 hyperactivation and Rab7 phosphorylation, promoting aberrant fusion and mixing of endosomal compartments. Consequently, impaired Rab7 function compromised the integrity of the endolysosomal membrane, releasing lysosomal enzymes and inducing widespread ELN dysfunction. Discussion: Our findings reveal a previously unrecognized mechanism in AD, establishing a novel axis linking Aβ, Rab GTPases, and endolysosomal network (ELN) dysfunction. Defining the critical Rab GTPases and their modulators in this pathway could open new avenues for therapeutic development in AD and DS-AD.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.06

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

Support: FCT PD/BD/135271/2017
NIH Intramural Research Program

Title: Chronic stress triggers extracellular vesicle release for the propagation of Tau pathology

Authors: *A. AMORIM GOMES[1,2], C. J. NOGUERAS-ORTIZ[1], C. SOARES-CUNHA[2], J. SILVA[2], B. COIMBRA[2], M. SAMIOTAKI[3], D. KAPOGIANNIS[1], N. SOUSA[2], C. WAITES[4], I. SOTIROPOULOS[5,2];
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Abstract: Despite considerable progress in our understanding of Alzheimer's disease (AD) pathogenesis, its initiating molecular events remain poorly defined. Clinical and preclinical evidence indicates that stressful lifetime experiences and increased levels of glucocorticoids (GC), the major stress hormones, are associated with increased risk of AD and accelerate disease progression. Our previous work shows that chronic stress/GC trigger pathogenic mechanisms of AD by increasing the accumulation of amyloid-beta extracellularly and hyperphosphorylated aggregation-prone Tau intracellularly. The latter is described to propagate in a stereotypical way between anatomically connected brain areas as disease progresses. Recent evidence supports small extracellular vesicles (EV) as propagators of pathological Tau among neurons in AD. However, it remains unclear whether and how stress contributes to the spreading and propagation of Tau pathology. Herein, we exposed Thy-Tau22 mice, which express human mutated Tau (G272V, P301S) under the Thy1.2 promotor, to a 4-week long chronic stress paradigm resulting in the exacerbation of Tau phosphorylation and its accumulation within the hippocampus, as well as the aggravation of cognitive deficits, anxiety and depressive-like behaviours. Simultaneously, chronic stress led to an increase of the release of EVs loaded with phosphorylated and oligomeric Tau. Proteomic analysis of both brain and brain-derived EVs revealed that the proteome of EVs obtained from stressed mice reflected the brain changes induced by stress in the brain, supporting their biomarker potential. In addition, the use of an exosome biogenesis inhibitor, GW4869, attenuated the stress-driven increase of brain EVs and Tau accumulation highlighting the important contribution of small EVs in the mechanisms through which chronic stress precipitates AD-related Tau pathology. Together this data provides a framework through which chronic stress and EVs contribute to the progression of Tau pathology. The detailed understanding of AD pathogenic mechanisms and their activation by clinically-relevant precipitating factors, such as chronic stress, is of paramount importance for the development of disease-modifying treatments.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.07

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

Support: NHI/NIA R01AG07313302 to GT

Title: Distinct Tau Oligomer Polymorphs in Circulating Plasma-Derived Extracellular Vesicles Associate with Alzheimer's Disease Vulnerability and Resilience in Individuals with Mild Cognitive Impairment

Authors: *M. MARCATTI[1], A. FRACASSI[1,2], W.-R. ZHANG[1], S. BUDHWANI[1], N. N. BHATT[1], B. KRISHNAN[1], R. KAYED[1], G. TAGLIALATELA[1,2];
[1]UTMB, Galveston, TX; [2]Moody Brain Hlth. Inst., Galveston, TX

Abstract: Alzheimer's disease (AD) often begins with mild cognitive impairment (MCI), yet some individuals progress to dementia while others remain cognitively stable. The mechanisms underlying these divergent trajectories remain poorly understood. Soluble tau oligomers (TauOs) are major mediators of synaptic dysfunction and neurodegeneration and can adopt distinct polymorphic conformations with unique biochemical and pathological properties that can contribute to vulnerability or resilience to cognitive decline. Plasma brain-derived extracellular vesicles (pl-BDEVs) provide minimally invasive access to CNS-derived cargo, enabling longitudinal investigation of TauO polymorphs in living individuals. Beyond providing insight into disease mechanisms, TauO signatures detected in pl-BDEVs may serve as candidate biomarkers of future disease progression. In this study, we analyzed plasma extracellular vesicles (pl-EVs) from longitudinal samples of participants in the Texas Alzheimer's Research and Care Consortium (TARCC), initially diagnosed with MCI and later classified as vulnerable (MCI-to-AD) or resilient (stable MCI). We characterized pl-EVs by nanoparticle tracking analysis, western blot (CD63, CD9, CD81), and electron microscopy. TauOs were immunoprecipitated and characterized by proteinase K (PK) digestion, seeding assay, atomic force microscopy (AFM), and western blot. Toxicity was evaluated in SH-SY5Y cells and human cortical synaptosomes. In parallel, brain-derived TauOs (BDTOs) were immunoprecipitated from immunomagnetically enriched CNS-derived pl-BDEVs. We identified distinct PK digestion patterns, seeding ability, morphology, and toxicity between TauOs from vulnerable and resilient MCI individuals, as well as different distributions across CNS-derived EVs. These findings identify conformationally distinct TauO polymorphs associated with future vulnerability and resilience to AD. Differences in biochemical, biophysical, and biological properties, together with distinct distributions across CNS-derived EV populations, suggest that TauO structural diversity may contribute to molecular pathways underlying neurodegeneration or resilience. Importantly, the detection of these signatures in accessible plasma brain-derived EVs highlights their potential as minimally invasive biomarkers for predicting divergent clinical trajectories. Together, these results provide a foundation for future mechanistic studies of TauO biology and for the development of blood-based biomarkers capable of predicting AD vulnerability and resilience.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

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

Support: National Institute on Aging of the National Institutes of Health under Award Number 5R01AG073133-05
National Institute on Aging of the National Institutes of Health under Award Number 5R21AG089708-02
Moody Brain Health Institute at the University of Texas Medical Branch

Title: A novel tau mutation associated with cognitive resilience to Alzheimer's disease neuropathology

Authors: M. MARCATTI[1], B. TUMURBAATAR[3], J. GUPTARAK[3], S. KADAMANGUDI[4], A. XIII[6], A. FRACASSI[5], R. KAYED[3], M.-A. MICCI[7], A. LIMON[2], ***G. TAGLIALATELA**[8]; [1]Neurol., UTMB, Galveston, TX; [2]Neurol. and Mitchell Ctr. for Neurodegenerative Dis., UTMB, League City, TX; [3]Neurol., [4]Mitchell Ctr. for Neurodegenerative Dis., [5]Mitchell Ctr. for Neurodegenerative Diseases, Dept. of Neurol., Univ. of Texas Med. Br., Galveston, TX; [6]Moody Brain Hlth. Institute, Univ. of Texas Med. Branch, Galveston, TX, Gavleston, TX; [7]Dept. of Anesthesiol., Univ. of Texas, Galveston, Dickinson, TX; [8]Univ. of Texas Med. Br. Dept. of Neurology, Moody Brain Hlth. Inst., Galveston, TX

Abstract: Aims:
Non-demented with Alzheimer's neuropathology (NDAN) individuals remain cognitively intact despite extensive Alzheimer's disease (AD) pathology. We investigated whether an NDAN-associated tau mutation contributes to formation of a non-toxic tau oligomer polymorph associated with cognitive resilience.
Methods:
Brain-derived tau oligomers (BDTOs) isolated from AD and NDAN hippocampi were characterized using proteinase-K digestion, atomic-force microscopy, biosensor aggregation assays, electrophysiology, and neuronal toxicity assays. MAPT sequencing was performed on AD and NDAN specimens. Recombinant wild-type (WT) and S305R tau oligomers were generated and assessed for biochemical and functional properties.
Results:
NDAN-BDTOs displayed increased protease resistance, altered conformational profiles, larger aggregate morphology, and markedly reduced synaptic and neuronal toxicity compared to AD-BDTOs. Sequencing identified a somatic serine-to-arginine substitution at position 305 (S305R) in all NDAN cases examined. Recombinant S305R tau formed a distinct non-toxic oligomer polymorph and preserved synaptic function relative to WT tau oligomers. Importantly, WT tau exposed to S305R tau oligomers adopted biochemical and functional features resembling the NDAN-associated polymorph, including reduced toxicity.
Conclusions:
These findings identify a novel NDAN-associated tau mutation linked to formation of a non-

pathogenic tau oligomer polymorph associated with cognitive resilience despite AD neuropathology. Our data further suggest that pathogenic tau can be redirected toward a benign conformational state, supporting a new therapeutic framework based on biochemical conversion of toxic tau species.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

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

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Title: A C/EBPβ-AEP Proteolytic Cascade Promotes Cognitive Decline after Spinal Cord Injury via Spreading of APP/Tau Pathology

Authors: *Z. WU[1,2], L. CHENG[2];
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Abstract: Spinal cord injury (SCI) is associated with long-term cognitive decline, but how a focal spinal lesion promotes brain proteopathy remains unclear. We tested whether activation of the CCAAT/enhancer-binding protein β (C/EBPβ)-asparagine endopeptidase (AEP) pathway links SCI to Alzheimer-like APP/Tau cleavage, fragment propagation, and memory impairment. Adult male and female C57BL/6 mice underwent T9 crush SCI or sham surgery; AEP conditional knockout mice and SCI mice treated with a brain-penetrant AEP inhibitor compound were used to test pathway dependence. We quantified AEP activity, C/EBPβ/Lgmn induction, APP C586 and Tau N368 fragments, Aβ and phospho-Tau pathology, neuroinflammation, synaptic integrity, neuronal survival, and behavior using biochemical assays, qPCR, western blotting, immunostaining, ELISA, Golgi staining, electron microscopy, bulk RNA-seq/scRNA-seq analysis, and fibril-spreading assays. SCI rapidly activated C/EBPβ-AEP signaling in the injured spinal cord, increased Tau N368 and APP C586 generation, and promoted Aβ deposition, phospho-Tau accumulation, and neuronal apoptosis. At 9 months after SCI, mice displayed impaired fear conditioning and object recognition, accompanied by elevated C/EBPβ-AEP activity in the cortex, hippocampus, thalamus, and striatum, as well as accumulation of Tau N368/APP C586 fragments, Aβ/phospho-Tau pathology, microglial activation, increased inflammatory cytokines, CA1 spine and synapse loss, and neuronal death. AEP deletion suppressed APP/Tau cleavage, attenuated amyloid/tau pathology and neuroinflammation,

improved locomotor recovery, preserved synapses, and protected learning and memory. AEP-generated Tau N368 and APP C586 bound directly; mixed Tau N368/APP C586 fibrils spread more efficiently along axons in microfluidic neuron cultures and caused greater LDH-releasing neurotoxicity than either fragment alone. Pharmacological AEP inhibition reduced C/EBPβ-AEP activity, APP/Tau fragment formation, Aβ/phospho-Tau signals, inflammatory mediators, and synaptic loss, and improved cognitive performance after SCI. These findings identify the C/EBPβ-AEP proteolytic cascade as a tractable spinal cord-to-brain mechanism underlying SCI-associated dementia-like pathology, and support AEP inhibition as a candidate disease-modifying strategy

Disclosures: Z. Wu: None. **L. Cheng:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.10

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

Support: NIH NINDS K99NS149164
AHA 23POST1025407

Title: Development of anovel adult human brain organoid culture system to modelAlzheimer’s disease

Authors: *C. C. RADA;
Medicine-Hematology, Stanford Univ., Redwood City, CA

Abstract: Development of a novel adult human brain organoid culture system to model Alzheimer’s disease Alzheimer’s disease (AD) is the most prevalent form of dementia and is characterized by progressive degeneration of neurons, leading to cognitive decline. Over 10% of people over age 65 have AD, highlighting an urgent need for innovative therapeutic targets. Previous research has focused on neuronal phenotypes of key AD hallmarks including neurofibrillary tangles and amyloid beta (Aβ) plaques. However, emerging evidence suggests that non-neuronal cells, including microglia and vascular cells, play a critical role in both the initiation and progression of AD. Yet limited investigation of vascular and microglial mechanisms in AD initiation and progression is partially attributed to a lack of appropriate experimental systems. Post-mortem samples represent end-stage disease, mouse models lack species specificity, and iPSC-derived organoids, while human, contain fetal-like neurons and lack integrated vasculature and microglia. Thus, this study developed a novel adult human brain organoid (ahBO) culture system from neurosurgical biopsies which co-preserves diverse cell types including adult neurons, oligodendrocytes, astrocytes, endothelial cells, pericytes, and microglia over hundreds of days without artificial reconstitution. AD phenotypes in non-diseased ahBOs were induced by recombinant Aβ monomers, which readily aggregated, induced neuronal

killing and exhibited differential phenotypes based on APOE allele status. Together, the ahBO system provides a robust in vitro platform that holistically captures the diversity of human brain cell types and enables mechanistic investigation of neurological disease.

Disclosures: C.C. Rada: None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.11

Topic:

Support: NIH Intramural Research Program

Title: APOE Isoform Dependent Differences in Mitochondrial Function, Morphology, and Oxidative Stress in Astrocytes Implications for Alzheimer's Disease

Authors: *T. DUBEY[1], P. J. YAO[2], P. NARAYAN[4], D. KAPOGIANNIS[3];
[1]Natl. Inst. on Aging, Baltimore, MD; [2]Lab. of Neurosciences, [3]LCI, NIA/NIH, Baltimore, MD; [4]NIH, Bethesda, MD

Abstract: Introduction:*Apolipoprotein E (APOE)* exists in multiple isoforms (*APOE2, APOE3, APOE4*, and the rare *APOE3* Christchurch (*APOE3cc*)) with *APOE4* being the strongest genetic risk factor for late onset Alzheimer's disease (AD) and *APOE2* and *APOE3cc* being protective. *APOE* is known to affect mitochondrial function and is highly expressed by astrocytes.Methods: We studied human isogenic iPSC-derived astrocytes expressing *APOE2, APOE3, APOE4* and *APOE3cc* alleles and interrogated proliferation rates, mitochondrial morphology, oxygen consumption rate (OCR), and oxidative stress (superoxide production), under basal conditions and following exposure to monomeric and oligomeric amyloid-beta (Aβ). Results:Under basal conditions, *APOE2* astrocytes had the highest proliferation rate; displayed elongated fused mitochondria; and lower basal and maximal OCR compared to *APOE4*. *APOE4* had the lowest proliferation rate; fragmented circular mitochondria; the highest basal and maximal OCR; and the highest superoxide production. *APOE3* and *APOE3cc* showed intermediate phenotypes. Treatment with oligomeric and monomeric Aβ did not change these mitochondrial phenotypes. However, both oligomeric and monomeric Aβ increased superoxide production of *APOE2, APOE3 and APOE3cc* astrocytes but not *APOE4* astrocytes. *APOE3cc* astrocytes had similar mitochondrial phenotypes as *APOE3* suggesting that non-mitochondrial mechanisms likely underlie its protective effect. Conclusions:Astrocytes carrying the AD-associated *APOE4* allele demonstrate slow cell proliferation, mitochondrial fragmentation and high OCR, whereas astrocytes carrying the protective *APOE2* allele show accelerated cell proliferation, elongated mitochondria and low OCR. These findings help bridge astrocytic mitochondrial function with *APOE* genotype and AD risk. Funding:This research was supported by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH authors are

considered Works of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

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Presentation Number: NANO39.12

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

Support: ALZDISCOVERY-1049110
NIH AG064016

Title: A humanized Aβ mouse model reveals APOE4-dependent neuroinflammation, cognitive deficits, and cerebral artery stiffness

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Abstract: Apolipoprotein E4 (*E4*) increases the chance of Alzheimer's disease (AD) diagnosis by up to 12-fold. However, an understanding of the mechanisms underlying this risk is limited by a lack of preclinical models that accurately reflect the effects of *E4* in the presence of humanized non-mutant *APP*. Therefore, we used the novel humanized Aβ(*hAβ*) mice to understand the contributions of the *E4* genotype to neural and vascular impairment. We hypothesized that, in the presence of *hAβ, E4* mice would exhibit greater memory impairments, neuroinflammation, oxidative stress, and cerebral artery stiffness than *E3*. In male and female *hAβ* mice that were homozygous for either the humanized *E4* or *E3* gene (*E4xhAβ* and *E3xhAβ,* 6 months of age, n=13), we evaluated cognitive function using the Novel Object Recognition test. Neuroinflammation we asssessed in the hippocampus by immunohistochemistry for activated microglia via ionized calcium-binding adaptor molecule 1 (Iba1). Expression of oxidative stress and inflammation genes nicotinamide adenine dinucleotide phosphate oxidase 2 (*Nox2*), and interleukin-1β (*Il1b*) were assessed with RT-qPCR in the cortex and cerebral arteries. Lastly, since arterial stiffness is associated with memory impairment, we measured the passive stiffness of the posterior cerebral arteries. Our cognitive test results revealed that the *E4xhAβ* mice spent less time with the novel object than the*E3xhAβ* mice, indicating a significant impairment in hippocampal-dependent recognition memory (p=0.044). The *E4xhAβ* mice had significantly higher Iba1 coverage than the*E3xhAβ* genotype (p=0.005). In the cortex, expression of pro-oxidant enzyme *Nox2*(p=0.002) was higher in the *E4xhAβ* mice than the *E3xhAβ* mice. In the cerebral arteries, pro-inflammatory *Il1b* expression was higher in the *E4xhAβ* mice than in the*E3xhAβ* mice (p=0.044). We found that the *E4xhAβ* mice had greater cerebral artery βstiffness

than the *E3xhAβ* mice (p=0.002). Overall, we found the *E4xhAβ* mice exhibited higher memory impairments, neuroinflammation, oxidative stress and cerebral artery stiffness which provides foundational evidence to investigate *E4*-dependentmechanisms of AD. Our findings support the use of the *APOExhAβ* mouse model without mutated amyloid-β to better understand the mechanistic drivers of AD.

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Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO39.13

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

Support: RO1AG069196
RO1AG074216

Title: ApoE4 reveals early lipidomic vulnerability along the olfactory-entorhinal axis in PS19 tauopathy mice

Authors: *S. ZAFAR[1], S. LIU[2];
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Abstract: Olfactory dysfunction is an early and consistent feature of Alzheimer’s disease (AD) and may reflect early pathological changes within the brain’s olfactory pathway. Apolipoprotein E4 (ApoE4), the strongest genetic risk factor for late-onset AD, has been associated with accelerated neurodegeneration, metabolic dysfunction, and early olfactory impairment. However, whether APOE4 produces early lipid remodeling along the olfactory-entorhinal axis during tauopathy progression remains unclear.In this study, male PS19 tauopathy mice expressing either ApoE3 [PS19(+/-)ApoE3(+/+); PSE3 (n=4)], or ApoE4 [PS19(+/-)ApoE4(+/+); PSE4 (n=4)] at 6 and 9 months of age were used for lipidomic profiling of olfactory bulb (OB), anterior olfactory nucleus (AON), and lateral entorhinal cortex (LEC). Lipidomic analyses were performed using UPLC-MS/MS. Quality assessment demonstrated strong analytical reproducibility with robust QC clustering and stable retention times across samples. Multivariate analyses (PCA and OPLS-DA) revealed clear lipidomic separation between PSE3 and PSE4 mice across all regions and ages, with prominent discrimination observed in LEC and OB.Differential lipid abundance analyses identified substantial region- and age-dependent alterations in PSE4 mice. At 6 months, LEC exhibited a higher number of altered lipids, followed by the OB and AON, suggesting early regional vulnerability. At 9 months, lipid dysregulation became more prominent within the OB and LEC. Glycerophospholipids represented the most affected lipid class across all regions and ages, particularly phosphatidylcholines (PC), phosphatidylethanolamines (PE), ether-linked

phospholipids, and lysophospholipids. Alterations were also detected in sphingolipids, including sphingomyelins and ceramide-related species. Fatty acyl subclasses also showed prominent alterations, particularly within the OB and LEC at 9 months. KEGG pathway analysis identified glycerophospholipid metabolism as the most recurrent and quantitatively represented lipid metabolic pathway, with additional enrichment of ether lipid metabolism, sphingolipid metabolism, linoleic acid metabolism, retrograde endocannabinoid signaling, and synaptic-related pathways in a region- and age-dependent manner, suggesting broad disruption of membrane lipid homeostasis and lipid-mediated neuronal signaling. Together, these findings demonstrate that ApoE4 drives early region-specific lipid remodeling across the olfactory-entorhinal axis in PS19 tauopathy mice.

Disclosures: S. Zafar: None. **S. Liu:** None.

Nanosymposium

NANO39: Alzheimer's Disease: Abeta, APOE, and Tau Mechanisms

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

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

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Title: Exogenously added apolipoprotein E alters cellular cholesterol and tight junction proteins of endothelial cells in the blood-brain barrier in an isoform-specific manner

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Abstract: The blood-brain barrier (BBB) is a selectively permeable interface formed by brain microvascular endothelial cells and maintained by cholesterol-rich tight junctions (TJs), that are characterized by marker proteins such as claudin, occludin, and ZO-1. Early reports indicated that the integrity of the BBB was severely affected in apolipoprotein E (apoE) knockout mice. ApoE is a major cholesterol transport protein in the brain and the plasma and exists as three major isoforms (apoE2, apoE3, and apoE4) in the human population with apoE4 strongly associated with Alzheimer’s disease and BBB dysfunction. We hypothesize that apoE plays a critical role in maintaining the BBB integrity by providing cholesterol to the TJs of the brain endothelial cells in an isoform-specific manner. Recombinant apoE2, apoE3, and apoE4 were complexed with POPC and cholesterol to form reconstituted HDL (rHDLc). Mouse brain endothelioma cells were treated with buffer or rHDLc complexes containing apoE2, apoE3, or apoE4. Intracellular levels of unesterified cholesterol were ~3x higher in rHDL-treated cells than

in PBS-treated controls. ApoE2-treated cells showed significantly higher levels of cholesterol compared to those treated with PBS ($p = 0.02$), apoE3/rHDLc ($p = 0.0004$), and apoE4/rHDLc (0.0004). Western blot analysis demonstrated that apoE/rHDL upregulates TJ marker proteins in an isoform-specific manner (apoE3 > apoE2 > apoE4) based on band intensities normalized to β-actin. To visualize externally supplied cholesterol, rHDL particles containing fluorescently labelled cholesterol (rHDLc*) were prepared using each apoE isoform. Confocal microscopy of cells treated with rHDLc* suggested greater cholesterol accumulation and co-localization with occludin in apoE2- and apoE3-treated cells than in apoE4-treated cells. Together, these findings suggest that apoE isoforms differentially regulate cholesterol delivery and TJ organization in brain endothelial cells, providing insight into mechanisms that may contribute to BBB dysfunction in neurodegenerative disease.

Disclosures: A. Anis: None. **M. Hernandez:** None. **V.N. Metkar:** None. **V. Narayanaswami:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

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Presentation Number: NANO40.01

Topic: D.04. Brain Injury and Trauma

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Falk Medical Research Trust

Title: Proliferative Reactive Astrocytes Promote Synaptic Preservation and Functional Recovery After Traumatic Brain Injury

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Abstract: Reactive astrocyte proliferation is a hallmark of astrogliosis after traumatic brain injury (TBI), yet the specific role of proliferative reactive astrocytes remains unclear. We recently discovered that platelet-derived growth factor receptor-α (PDGFRα) is transiently induced in reactive astrocytes after controlled cortical impact (CCI), providing a unique opportunity to selectively examine this astrocyte population. Based on preliminary evidence that proliferative reactive astrocytes express high levels of brain-derived neurotrophic factor (BDNF) and interact closely with synapses, we investigated whether these cells contribute to synaptic preservation and functional recovery after TBI. To selectively suppress reactive astrocyte proliferation, we generated conditional PDGFRα knockout (cKO) mice. Consistent with our previous findings, moderate TBI caused substantial synaptic loss throughout the hippocampus.

Importantly, loss of PDGFRα-dependent astrocyte proliferation further worsened synaptic degeneration, as indicated by a significant reduction in synaptophysin-positive puncta compared with injured control mice ($p < 0.01$). To determine whether this increased synaptic loss translated into functional deficits, we used inducible **GFAP-Cre^{ERT2}::PDGFRα$^{flox/flox}$** mice to eliminate proliferative reactive astrocytes after injury while minimizing developmental confounds. Behavioral assessment revealed that mice lacking proliferative reactive astrocytes displayed greater impulsive-like behavior following TBI, spending more time and traveling greater distances in the open arms of the elevated plus maze. To explore potential mechanisms, proliferative reactive astrocytes were labeled using GFP retrovirus. Confocal imaging demonstrated that surviving proliferative astrocytes extended processes that closely contacted and surrounded synaptophysin-positive synapses, consistent with participation in tripartite synaptic structures. In addition, proliferative reactive astrocytes expressed markedly higher levels of BDNF than neighboring non-proliferating astrocytes. Together, these findings suggest that proliferative reactive astrocytes are not simply a byproduct of injury but actively support synaptic integrity and functional recovery after TBI. Their neuroprotective effects may be mediated, at least in part, through astrocytic BDNF signaling, highlighting the PDGFRα-BDNF pathway as a promising target for therapies aimed at promoting circuit repair and recovery after brain trauma.

Disclosures: L.K. Pradhan: None. **F. Yuan:** None. **X. gao:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO40.02

Topic: D.04. Brain Injury and Trauma

Support: NIH grant R01NS133233

Title: PAD4-Dependent Neutrophil Extracellular Trap Formation Drives Cerebrovascular Thrombosis Following Traumatic Brain Injury.

Authors: *P. A. MUNEER[1], T. BARRIOS LIZON[2], S. BHOWMICK[3];
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Abstract: Traumatic brain injury (TBI) initiates a complex cascade of neurovascular events characterized by endothelial activation, blood-brain barrier disruption, leukocyte infiltration, and microvascular dysfunction. Emerging evidence suggests that neutrophil extracellular traps (NETs), extracellular networks of decondensed chromatin and granular proteins released by activated neutrophils, play a critical role in thromboinflammatory responses. However, the mechanisms linking NET formation to thrombosis after TBI remain largely unknown. In this study, we investigated whether TBI-induced NET formation promoted cerebrovascular

thrombosis through interactions with platelets, endothelial adhesion molecules, and procoagulant factors. Following injury, endothelial activation increased the expression of E-selectin and P-selectin, facilitating neutrophil-platelet adhesion through binding to P-selectin glycoprotein ligand-1 (PSGL-1) and promoting NET release. NETs subsequently served as a structural scaffold for platelet adhesion and aggregation while concentrating prothrombotic mediators, including von Willebrand factor (vWF), fibrinogen, and factor XII. In parallel, vascular injury exposed subendothelial collagen, triggering platelet activation and thromboxane production, which further amplified thrombus formation. We further examined the role of peptidyl arginine deiminase 4 (PAD4)-dependent histone citrullination in regulating NET generation and investigated how NETs interacted with platelet proteins and coagulation pathways to drive thrombosis following TBI. Using complementary *in vitro* and *in vivo* approaches, including genetic deletion of PAD4, we demonstrated that PAD4-mediated NET formation is a key contributor to platelet activation, thrombus formation, and microvascular occlusion after brain injury. NETs co-localized with platelet markers and procoagulant molecules within the injured cerebral vasculature, supporting their role as a platform for thrombus assembly. Collectively, these findings establish a mechanistic link between NET formation and cerebrovascular thrombosis and identify NET-driven thromboinflammation as an important contributor to secondary neurovascular injury following TBI. This work was supported by the NIH grant R01NS133233 to P. M. Abdul Muneer.

Disclosures: P.A. Muneer: None. **T. Barrios Lizon:** None. **S. Bhowmick:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

Location: WCC Rm 144

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Presentation Number: NANO40.03

Topic: D.04. Brain Injury and Trauma

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NJCBIR CBIR25IRG013
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The Veterans Bio-Medical Research Institute

Title: Sex and strain affect Morris Water Maze performance following blast-induced traumatic brain injury in mice.

Authors: *V. DELIC[1,2,3], I. M. BILUCK[1,3], K. E. MURRAY[1], A. E. DANIEL[1], T. P. COMINSKI[1], V. A. STIRITZ[1,3], B. J. PFISTER[4], K. D. BECK[1,2,3], B. A. CITRON[1,2,3]; [1]Res. & Develop., VA New Jersey Hlth. Care Syst., East Orange, NJ; [2]Pharmacology, Physiology, & Neurosci., Rutgers New Jersey Med. Sch., Newark, NJ; [3]Sch. of Grad. Studies, Rutgers Univ., Newark, NJ; [4]Dept Biomed Engin., New Jersey Inst. Technol., Newark, NJ

Abstract: Blast-induced traumatic brain injuries remain a significant problem among military personnel requiring greater attention. Mild blast exposures resulting in cognitive deficits and susceptibility to blast injury and the recovery rate can vary greatly. Model strains of mice that span 90% of the genetic diversity between laboratory strains were exposed to blast (180 kPa) and their responses compared across the 8 different strains and males and females of each strain. We previously reported some of the strain and sex specific gene dysregulations (that involved RNA-seq of 96 different hippocampi, n=3/group) in relation to startle and pre-pulse inhibition behavior. We have extended the gene expression analysis and have completed Morris water maze evaluations (n=12/group) of male and female C57BL/6J and 129S1/SvImJ strains out to 90 days post-injury. We found sex and strain dependent differences. For example, only male C57BL/6J mice displayed an increase in distance ($p<0.02$) and latency ($p<0.03$) to enter the platform area (spatial learning deficits) during intermediate learning sessions of the hidden platform stage 1-week post-injury. The male 129S1/SvImJ strain also displayed a learning deficit. Among the gene dysregulations, we found that Neurod6 was downregulated in male C57BL/6J (1.6 fold, $p=0.01$) and 129S1/SvImJ (1.9 fold, $p=0.003$) mice by the injury. Neurod6 is a transcription factor of the neuronal differentiation family that is important for granule cells of the hippocampal dentate gyrus. The information obtained provides a foundation for future studies to identify therapeutic targets that could result in improved outcomes for affected individuals.

Disclosures: V. Delic: None. **I.M. Biluck:** None. **K.E. Murray:** None. **A.E. Daniel:** None. **T.P. Cominski:** None. **V.A. Stiritz:** None. **B.J. Pfister:** None. **K.D. Beck:** None. **B.A. Citron:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

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Topic: D.04. Brain Injury and Trauma

Support: NJ CBIR Grant CBIR25IRG013
VA BLR&D Grant I01BX005015
VA RR&D Grant IK2RX003253
VA Research Career Scientist Award IK6BX006188

Title: Combined neuroprotective transcription factor modulation after repetitive closed head TBI

Authors: *B. A. CITRON[1,2,3], A. E. DANIEL[1], I. M. BILUCK[1,3], V. DELIC[1,2,3];
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Abstract: Repeated mild traumatic brain injury (mTBI) is a common injury among military personnel and veterans, as well as athletes. mTBI can produce persistent cognitive deficits, yet

the underlying cell-specific molecular alterations remain incompletely understood. This study investigated transcriptional changes following repetitive closed head mTBI and evaluated the therapeutic potential of combined treatment of tert-butylhydroquinone (tBHQ) and pioglitazone, activators of the Nrf2 and PPARγ pathways. Repetitive mTBI was induced in 8 male mice using a closed-head weight-drop model consisting of four weekly impacts delivered by a 30 g weight, followed by a 50 g weight drop. Six weeks after the final injury, mice received chow containing tBHQ and pioglitazone for 4 weeks. Brains were collected ten weeks after the final injury and analyzed using the 10x Genomics Xenium spatial transcriptomics platform for 297 genes to determine expression responses to the injury and treatment. Repetitive mTBI induced a variety of significant cell-type-specific transcriptional alterations. For example, in dentate gyrus granule cells of the hippocampus, expression of Sox11 (SRY (sex determining region Y)-box 11), a regulator of nervous system development and gene expression, was downregulated 20% ($p=0.011$) after injury and restored by treatment ($p=0.032$). Astrocytes exhibited 40% reduced expression of Ebf3 (Early B-cell factor 3), a transcription factor involved in neurodevelopment and neuronal maturation, after injury ($p=0.002$), which was reversed following treatment ($p=0.016$). Conversely, Gadd45a (Growth arrest and DNA damage-Inducible 45 alpha), a mediator of cellular stress and DNA damage responses, was elevated 1.34 fold after injury ($p=0.012$) and reduced by treatment ($p=0.023$). In microglia, Ntsr2 (Neurotensin receptor 2), a G protein-coupled receptor implicated in fear memory, decreased after injury ($p=0.027$) by approximately 20% and restored following treatment ($p=0.0058$). Collectively, these findings demonstrate that repetitive closed-head mTBI produces long-lasting cell-specific transcriptional dysregulation in the hippocampus and that treatment in the chronic phase normalizes injury-associated molecular signatures. These results support Nrf2 and PPARγ activation as a potential therapeutic strategy for chronic mTBI.

Disclosures: B.A. Citron: None. **A.E. Daniel:** None. **I.M. Biluck:** None. **V. Delic:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

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Presentation Number: NANO40.05

Topic: D.04. Brain Injury and Trauma

Support: Merit Review Award Number 1I01BX006223-01A1 from the U.S. Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service
Merit Review Award Number I01 RX003506 from the U.S. Department of Veterans Affairs Rehabilitation R&D (RR&D) Service
Florida Department of Health #25K06
American Heart Association (AHA; 25TPA1476464)

Title: Nicotine and oral contraceptive exposure exacerbate cognitive impairment after mild traumatic brain injury in female rats.

Authors: *H. SHARMA[1], J. SANCHEZ-MOLANO[2,3], W. J. MORENO[2,3], I. CABEDA DIAZ[1], H. M. BRAMLETT[2,3,4], A. P. RAVAL[1,3,4];
[1]Neurol., [2]Neurolog. Surgery, [3]Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL; [4]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL

Abstract: Nicotine exposure through electronic cigarettes (EC) and oral contraceptive (OC) use are prevalent among women of reproductive age; however, their combined impact on traumatic brain injury (TBI) outcomes remains poorly understood. We tested the hypothesis that nicotine and OC exposure interact to exacerbate mild TBI outcomes through transcriptomic alterations in the female brain. Adult female rats were exposed to EC aerosol generated from 5% nicotine JUUL pods using the EcigAero Aerosol Exposure System for 16 days (16 episodes/day over 8 hours). Control animals were exposed to air. A separate cohort received OC or placebo during the 16-day EC exposure period. On day 17, rats underwent mild fluid percussion injury (1.5-1.7 atm) or sham surgery and survived for either 16 or 30 days. Cortical tissue collected 16 days post-TBI was subjected to RNA sequencing. Animals surviving for 30 days underwent behavioral assessment, including motor testing using the cylinder task and cognitive evaluation using the Morris water maze, followed by histopathological analysis. Cortical contusion volume, was significantly greater in EC-exposed rats compared with air-exposed controls, indicating that chronic nicotine exposure exacerbates structural brain injury. Transcriptomic analysis revealed marked cortical gene expression changes following combined EC+OC exposure, with 737 genes upregulated and 536 downregulated. Gene ontology analysis demonstrated enrichment of pathways involved in dopaminergic and serotonergic signaling, calcium-regulated exocytosis, SNARE complex assembly, and endoplasmic reticulum calcium homeostasis. The combined EC+OC exposure worsens TBI outcomes in females, highlighting an underrecognized risk factor relevant to women's brain health.

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Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO40.06

Topic: D.04. Brain Injury and Trauma

Title: Targeting T regulatory cells to Modulate Neuroinflammation and Neurobehavioral Impairment in Pediatric Repetitive Mild TBI

Authors: *K. SHUMILOV BARTENEV[1], L. ARELLANO[1], W. BERNHARDT[1], J. E. GREER[3], J. P. MCALLISTER[2], M. GARCIA BONILLA[2], K. M. JACOBS[1], D. LIMBRICK[1];
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Abstract: Pediatric repetitive mild traumatic brain injury (rmTBI) is a major public health concern with links to cognitive dysfunction, anxiety, and depression. The underlying mechanisms of neuroinflammation in pediatric rmTBI are not well understood. The objective of this study was to examine the impact of T regulatory cells (T_{regs}) and subsequent neuroinflammation on white matter (WM) disruption and neurobehavior outcomes. Our Central Hypothesis is that pediatric rmTBI induces white matter disruption and long-term neurobehavioral alterations via a T_{reg}-mediated inflammatory pathway. Our prior study (Shumilov et al., 2026) using p P21 mice with a weekly rmTBI frequency have shown T cell dependent increased infiltration of activated macrophages, CD8/CD4 T cells, as well as increased density of astrocytes and microglia. Using the same juvenile rmTBI model, two months after injury, diffusion basis spectrum imaging was used to analyze WM structural disruption, light-dark box, and Barnes maze behavioral tests were performed to evaluate memory and anxiety-like behavior. Preliminary data indicates that two months following rmTBI and Treg depletion, subjects exhibited significant memory impairments. Notably, the depletion of T_{regs} exacerbated the infiltration of CD4 T cells. Furthermore, decreased Fiber Fraction in the CC was detected two weeks after injury. These findings suggest that rmTBI triggers WM disruption and neurobehavioral impairments, probably modulated by T_{regs}. Our future goal is to develop noninvasive therapy to stimulate T_{regs} proliferation, avoid disruption of WM connectivity, and prevent neurobehavioral impairments, leading to improved treatment and reducing the long-term burden of children with rmTBI.

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Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

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Presentation Number: NANO40.07

Topic: D.04. Brain Injury and Trauma

Support: ONR N00014-22-1-2828
ONR N00014-23-1-2006

Title: Ionic gradient handling outweighs excitotoxicity in driving the immediate calcium response to moderate brain injury

Authors: *J. A. SERGAY[1], N. SCHICK[2], A. HAI[3], C. FRANCK[4];
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Abstract: Traumatic brain injury (TBI) disrupts neuronal calcium signaling within seconds of mechanical loading. Yet the pathways that drive this hyperacute response remain poorly defined, especially at the mild loading levels most relevant to concussion. The prevailing view centers on glutamatergic excitotoxicity, in which N-methyl-D-aspartate (NMDA) receptor activation floods neurons with calcium, but this idea has rarely been tested at single-cell resolution in the first minutes after a controlled mechanical injury. In this exploratory study, we applied a controlled uniaxial stretch ($\varepsilon = 0.3$ at 25 s^{-1}) to primary rat cortical neuron-astrocyte co-cultures (postnatal day 0-1, mixed-sex cultures) and imaged single-cell calcium (Fluo-4) for the two minutes before and after injury. We selectively removed extracellular Ca^{2+}, Na^{+}, or K^{+}, or blocked NMDA receptors with MK-801, each compared against sham and stretched controls (N = 4-5 cultures per condition). At severe loading, we previously found strong, rate-dependent suppression of activity. Moderate stretch behaved differently: bulk calcium-transient rate, decay, and amplitude barely moved. The earliest effects appeared instead in two readouts, neuronal participation and resting (basal) calcium. Removing extracellular K^{+} was the only manipulation that reduced the number of active neurons after stretch. The stretch-evoked rise in basal calcium was even more revealing. It persisted when extracellular Ca^{2+} was removed and when NMDA receptors were blocked yet vanished in Na^{+}-free and K^{+}-free media. Together, these results point away from glutamatergic influx and toward integrated $Na^{+}/K^{+}/Ca^{2+}$ ion handling, such as gradient-driven Na^{+}/Ca^{2+} exchange and Na^{+}/K^{+}-ATPase load, as the driver of the moderate-injury response. These findings suggest that the dominant hyperacute mechanism may shift with injury severity, and they nominate ion-transport machinery as a candidate target for monitoring and protecting the brain after mild TBI. To pinpoint the underlying fluxes, ongoing work couples these data to a biophysical electro-diffusive (Poisson-Nernst-Planck) model of Na^{+}, K^{+}, and Ca^{2+} transport.

Disclosures: J.A. Sergay: None. **N. Schick:** None. **A. Hai:** None. **C. Franck:** None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

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Presentation Number: NANO40.08

Topic: D.04. Brain Injury and Trauma

Support: NIH R01 NIMH 7R01MH129732-04
NIH RF1NS128739
CU Anschutz SOM ASPIRE Program

Title: Rethinking Traumatic Brain Injury as a Spatial Transcriptomic State Shift

Authors: *A. CRUZ-MARTIN;
Univ. of Colorado, Anschutz Med. Campus, Denver, CO

Abstract: Traumatic brain injury (TBI) is often conceptualized as a focal lesion followed by secondary cellular responses, but the molecular consequences of injury are likely organized

across anatomical space and distributed cell-state programs. Here, we asked whether Xenium-scale spatial transcriptomics could reveal TBI as a spatial transcriptomic state shift across the mouse brain. Adult C57BL/6 mice were subjected to sham surgery or closed-head injury using the CHIMERA model, and brain tissue was collected at acute post-injury time points. Sagittal brain sections were profiled using the 10x Genomics Xenium platform with a ~5,000-gene panel. To analyze these high-density spatial transcriptomic data without relying on predefined cell boundaries, we adapted segmentation-free factor modeling approaches, including FICTURE/Punkst-style workflows. Transcript coordinates were tiled, binned into hexagonal spatial units, harmonized across samples, and modeled using latent topic/factor inference. We also implemented region-aware cropping to preserve anatomical context while reducing off-target tissue signal, enabling focused analysis of hippocampal and cortical regions.Segmentation-free modeling recovered large-scale anatomical organization, including cortical domains, hippocampal subregions, cerebellar regions, and white matter-associated programs. In hippocampal regions of interest, unsupervised factors mapped onto canonical cell identities, including inhibitory interneuron subclasses, dentate gyrus granule neurons, astrocyte-associated programs, and rare proliferative or activity-associated states. Multisample topic modeling enabled consistent inference of spatial programs across sham and TBI samples while preserving sample identity for downstream comparison. Acute TBI was associated with increased representation of glial/complement-related and vascular/endothelial-associated programs, consistent with early astrocyte and neurovascular responses. In males, 48 h post-injury was also associated with an elevated neuronal plasticity/excitability-like program, suggesting that TBI induces sex- and time-dependent shifts in neuronal state programs in addition to glial and vascular responses.Together, these data support a view of TBI as a spatially organized transcriptomic state shift rather than a uniform lesion response. Segmentation-free spatial modeling provides a scalable framework for mapping injury-associated cell identities and cell states across anatomical regions, and may help identify molecular programs linked to acute pathology, sex-specific vulnerability, and circuit-level dysfunction.

Disclosures: A. Cruz-Martin: None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO40.09

Topic: D.04. Brain Injury and Trauma

Title: Healthy brain aging in TBI survivors at risk for Parkinson's disease and the dementias

Authors: *P. F. ARAVICH;
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Abstract: The US Centers for Medicare and Medicaid Services recognized TBI as a chronic health condition starting January 2025. Meanwhile, for years the US Department of Veterans

Affairs has effectively considered TBI a chronic condition with its 100% Permanent and Total Disability Ratings. More people---including combat Veterans---are living with TBI than ever before. The CDC argues greater attention should focus on the "long-term health and well-being" of TBI survivors---an issue also stressed by TBI Model Systems of the National Institute on Disability, Independent Living, and Rehabilitation Research. This unmet need relates to, e.g., increased risks for the dementias and Parkinson's disease. The World-Wide FINGERS Network and its related US Pointer Study together with the Lancet Dementia Commission reported lifestyle and other modifiable risk factors for the dementias, which overlap with Parkinson's risk, are amenable to TBI survivors, and are consistent with a CDC TBI public health model. Unfortunately, significant silos exist between TBI, Parkinson's and dementia efforts, and there is a need to promote greater awareness of the benefits of lifestyle factors for healthy brain aging. This presentation will review relevant lifestyle and modifiable risk factors. It will then propose a TBI Survivor Healthy Brain Aging Consensus Conference. Partners will include TBI, Parkinson's, dementia, behavioral health, and Veterans experts. The goal will be to develop a consensus statement with evidence-based action items to promote healthy brain aging in TBI survivors and reduce neurodegenerative disorder risks.

Disclosures: P.F. Aravich: None.

Nanosymposium

NANO40: Traumatic Brain Injury: Mechanisms and Therapies

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 8:00 AM - 10:30 AM

Presentation Number: NANO40.10

Topic: D.04. Brain Injury and Trauma

Support: DoD-Traumatic Brain Injury and Psychological Health Research Program TP230226

Title: Development of an Ultra-Selective DYRK1A Inhibitor as an Acute Therapeutic Strategy for Repeated Head Trauma

Authors: *B. C. MOUZON[1], D. PARIS[2], S. FERGUSON[3], F. C. CRAWFORD[1];
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Abstract: Background: Dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) phosphorylates Tau at residues such as Thr231, priming Tau for pathological hyperphosphorylation after brain injury. DYRK1A also regulates inflammatory signaling and cellular responses to DNA damage, processes activated early following brain injury. Targeting DYRK1A during the acute post-injury window may therefore mitigate secondary injury mechanisms and limit the progression of tau pathology. **Methods:** Human Tau (hTau) transgenic mice received five repeated head injuries RHI administered 48 hours apart. Treatment with the ultra-selective DYRK1A inhibitor SM15685 (10 or 20 mg/kg) began 1 hour after the final injury

and continued daily for 21 days. Behavioral assessments included Rotarod, Barnes Maze, EPM, and optomotor response. Neuropathology evaluated GFAP, Iba1, and oligodendrocyte-associated tau pathology. Plasma biomarkers (GFAP, NFL, and total Tau) were quantified using the MSD S-PLEX assays. **Results:** Injured animals displayed persistent motors and visual deficits. Treatment with SM15685 improved motor coordination, with injured mice approaching sham performance by Day 17. SM15685 also improved visual tracking responses and partially normalized behavioral alterations in the EPM. Histological analyses revealed reduced microglial activation and astrocytosis in the brainstem, along with reductions in oligodendrocyte-associated p-tau. Plasma biomarker analysis demonstrated reduced GFAP and neurofilament light levels during the sub-acute phase following treatment. **Conclusion:** Acute DYRK1A inhibition with SM15685 attenuates early neuroinflammation, axonal injury biomarkers, and tau pathology while improving functional outcomes after RHI. These findings support DYRK1A inhibition as a promising acute therapy to limit secondary injury and warrant further study of its effects on chronic RHI outcomes.

Disclosures: B.C. Mouzon: None. **D. Paris:** None. **S. Ferguson:** None. **F.C. Crawford:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO41.01

Topic: E.06. Vision

Support: NIH ZIAMH002909

Title: Cortical and subcortical correlates of candid human and illusory faces revealed with 7T fMRI

Authors: *S. G. WARDLE[1,2], J. TAUBERT[3], M. UDEOZOR[4], C. I. BAKER[2];
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Abstract: Face pareidolia is the perception of illusory faces in inanimate objects. Although face pareidolia engages areas of ventral occiptotemporal cortex in the human brain and emotional expressions are attributed to illusory faces by human observers, it is unknown whether the human amygdala responds to face pareidolia, and whether its response is mediated by emotional expression. In addition, previous studies examining the cortical and amygdala response to expressive human faces have typically used controlled, posed expressions rather than naturalistic expressions that are highly variable in visual properties. Here we measured the BOLD response to human faces and illusory faces in the human brain with 7 Tesla fMRI (1x1x1mm voxels, TR = 2s, 56 slices, partial volume). Human participants (N = 21) viewed photographs of 21 human faces with natural and candid emotional expressions (happy, angry, and neutral), and 21 examples of face pareidolia with the same expressions. For each illusory face, we included a

matched control image of a similar object without an illusory face (21 images). Each of the 63 images was shown once per run for 300ms with a 5.7s ISI; participants completed 6-7 runs. We used a 1-back task to maintain attention in the scanner. We defined face-responsive regions of the amygdala and cortical face areas in occipitotemporal cortex using independent localizer runs containing different expressive face and object photographs. Using multivariate pattern analysis, we were able to successfully decode human faces versus objects from patterns of BOLD activation in all cortical (FFA, OFA, pSTS) and subcortical (amygdala) regions of interest. However, illusory faces could only be decoded from objects in the cortical brain regions and not in the amygdala. Only in the pSTS was there any evidence for the decoding of emotional expression. Overall, univariate analyses of individual images showed that the magnitude of the BOLD response was modulated by the presence of a face (either real or illusory) rather than by the emotional expression across both cortical and subcortical face-preferring regions. There was no evidence for a shared representation of emotional expression or valence across different faces in cortical face-responsive regions or face-selective voxels of the human amygdala. Together the results demonstrate that while face-preferring regions show a high degree of tolerance for the visual features that define a face, this is not the case for emotional expression in either subcortical or cortical regions. The results are important in constraining models of face perception, particularly those that propose a fast subcortical route for face processing.

Disclosures: S.G. Wardle: None. **J. Taubert:** None. **M. Udeozor:** None. **C.I. Baker:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Presentation Number: NANO41.02

Topic: E.06. Vision

Support: R01NS099429
R01EB034919
CCSN Fellowship

Title: Motion-Energy Modeling Predicts and Decodes Naturalistic Visual Representations in Mouse Cortex

Authors: *Z. LI[1,2], S. CHEN[1,2], W. FEHNER[2,3], A. BICE[2], S. BICE[2], J. P. CULVER[2,3,1];
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Abstract: Introduction: Natural vision requires animals to extract behaviorally relevant information from dynamic scenes, yet mouse visual cortex is often studied with simplified stimuli that isolate receptive-field properties but omit natural spatiotemporal structure. We asked whether a motion-energy encoding framework can preserve the complexity of natural movies while retaining interpretable links to classical visual features. **Methods**: Awake head-fixed GCaMP4.3 mice (n=5) underwent one-photon wide-field calcium imaging during natural-movie

viewing. Each mouse viewed 90 min of unique training movies and 10 repeats of a held-out 9-min test movie. Movies were transformed into 6,555 motion-energy features, and pixelwise cortical responses were modeled with L2-regularized linear regression and temporal delays. Performance was evaluated on held-out data using prediction accuracy, predicted-versus-measured correlation, clip decoding, and recovery of retinotopic and directional tuning structure. **Results**: As in Fig. 1, repeated natural movies evoked reliable stimulus-locked activity (A). Compared with checkerboard-based models, natural-movie models engaged broader cortical territory, including visual, retrosplenial, and associative regions, suggesting that naturalistic stimuli recruit distributed networks beyond classical visual areas (B). Motion-energy models generalized to novel movies, captured spatial response patterns, and supported above-chance decoding of held-out clip identity across multiple temporal segmentations (C-D). Predicted responses recovered functional organization, including retinotopic maps and direction tuning, linking model performance to established visual physiology (E-H). **Conclusion**: Motion-energy modeling provides a scalable and interpretable approach for predicting and decoding naturalistic visual responses in mouse cortex. This framework connects ecologically valid visual input to distributed cortical dynamics and provides a foundation for cellular, semantic, and cross-species studies of natural vision.

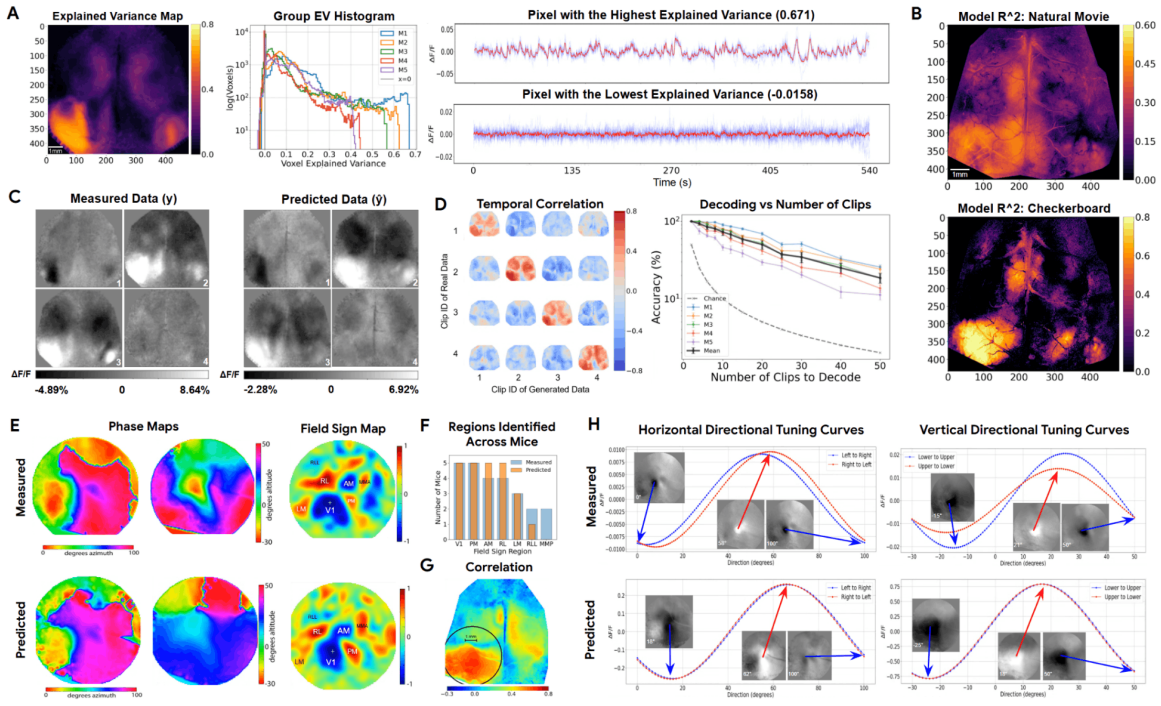


Fig. 1. Motion-energy modeling encodes, predicts, and decodes cortical responses to naturalistic visual stimuli in the mouse cortex. (A) Explained variance (EV) of cortical responses to the 9-min test movie across 10 repeats. **Left:** spatial EV map for a representative mouse. **Middle:** group histogram of pixelwise EV across mice. **Right:** ΔF/F time courses from the pixels with the highest and lowest EV, illustrating strong stimulus-locked reliability in high-EV regions. **(B)** Model generalization performance quantified by pixelwise R^2 maps. **Top:** motion-energy model trained on 90 min of natural-movie data and evaluated on a held-out 9-min test movie. **Bottom:** model trained and tested on flickering checkerboard data (train:test = 5:5 repeats). **(C)** Representative cortical activity frames from the held-out 9-min test movie, shown at 2.25-min intervals. **Left:** measured responses. **Right:** model-predicted responses. Predicted activity recapitulates major spatial response patterns in the measured data. **(D) Left:** clip-by-clip temporal correlation matrix between predicted and measured responses, showing higher correlations for matched clips (diagonal) than mismatched clips (off-diagonal). **Right:** group model-based decoding accuracy as a function of the number of clips. The 9-min held-out movie was segmented into 2–50 clips (270–10.8 s per clip). Decoding remained well above chance across segmentation levels, although performance declined as clip duration decreased and the number of candidate classes increased. **(E)** Retinotopic maps derived from measured and predicted data. Azimuth, altitude, and field-sign maps generated from model-predicted responses closely resembled those derived from measured activity. **(F)** Visual field-sign regions identified across mice from measured and predicted maps. Lower visual areas, including V1, PM, AM, and RL, were recovered most consistently. **(G)** Spatial map of temporal correlation between measured and predicted responses to the 9-min natural movie. The circle indicates the field of view used for retinotopic mapping. **(H)** Directional tuning curves from a representative V1 pixel for horizontal and vertical motion axes, shown for measured (**top**) and predicted (**bottom**) responses. Insets show representative stimulus frames corresponding to baseline and preferred-direction epochs.

Disclosures: Z. Li: None. **S. Chen:** None. **W. Fehner:** None. **A. Bice:** None. **S. Bice:** None. **J.P. Culver:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Presentation Number: NANO41.03

Topic: E.06. Vision

Support: This work was supported by internal research funds from Georgetown University Medical Center to TTL.

Title: High-frequency transcranial random noise stimulation over bilateral hMT+ accelerates motion perceptual learning in post-stroke visual field loss

Authors: *K. MOON[1], S. MONTOYA[1], B. RISPOLI[1], A. BIST[1], S. ABOOBUCKER SIDIQ[1], B. OSBORNE[2], T. T. LIU[1];
[1]Visual Perception and Plasticity Lab, Dept. of Neurol., Georgetown Univ., Washington, DC; [2]Departments of Neurol. and Ophthalmology, Medstar Georgetown Univ. Hosp., Washington, DC

Abstract: Visual field loss is a common consequence of stroke-related damage to cortical visual pathways, yet effective rehabilitation options remain limited. Perceptual learning (PL)-based interventions can partially restore visual function in cortically blind patients, but improvements typically require months of intensive training. High-frequency transcranial random noise stimulation (hf-tRNS), a noninvasive neuromodulation technique, has been shown to enhance PL in healthy adults and improve motion processing in chronic cortically blind patients following 10 days of training. As part of the broader VIBRANT (Vision Improvement through Behavioral Rehabilitation and Neuroplasticity Training) study, we investigated whether a condensed two-day hf-tRNS protocol over bilateral human middle temporal complex (hMT+) can enhance motion direction discrimination when paired with motion-based PL training in stroke patients with visual field loss. We used a double-blind, randomized, sham-controlled crossover design. Four stroke patients with visual field loss (3 male, 1 female) participated. Each participant completed both hf-tRNS and sham conditions, each consisting of two consecutive days of stimulation and training separated by a washout period of approximately one week. Each day included two 18-minute stimulation sessions separated by a 10-minute break, yielding four sessions per stimulation condition. During stimulation, participants performed a peripheral motion direction discrimination task within their perimetrically defined blind field, judging the direction (upward vs. downward) of random-dot motion stimuli. We observed converging evidence of enhanced learning during hf-tRNS relative to sham stimulation using linear mixed-effects models. Improvement in motion direction discrimination accuracy from the first to the

last training block was more than 20% greater during hf-tRNS than sham stimulation ($p < 0.05$). In addition, session-level performance exhibited a significantly steeper positive learning slope during hf-tRNS than during sham stimulation ($p < 0.01$). Together, these preliminary findings suggest that a condensed two-day hf-tRNS protocol over bilateral hMT+ can accelerate motion perceptual learning in individuals with post-stroke visual field loss. Ongoing work within the VIBRANT study will assess whether these short-term gains translate to broader changes in visual function and neuroimaging indices of training-related neuroplasticity.

Disclosures: K. Moon: None. **S. Montoya:** None. **B. Rispoli:** None. **A. Bist:** None. **S. Aboobucker Sidiq:** None. **B. Osborne:** None. **T.T. Liu:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Presentation Number: NANO41.04

Topic: E.06. Vision

Support: ISF grant 1462/23 to SGD

Title: NOW, SOON, or LATER ? Egocentric time, not information type, organizes three visual pathways

Authors: *S. GILAIE-DOTAN[1,2];
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Abstract: The dominant role of any sensory system is to allow the organism to sense its environment (“NOW”), plan its potential (re)action according to its goals given the current surroundings and events (“SOON”), and learn (acquire knowledge) from current experiences for the future (“LATER”). While these are critical for survival (whether the organism is standstill, moving slowly or extremely fast through its environment), the prevailing 2-pathway model of human visual system organization mainly concerns and is based on data from organisms that are confined to one place in their environment. Importantly, the speed at which we move through the environment probably dictates and qualitatively changes “the what” and “the where” our visual system is tuned to (e.g. when running or driving but not when seated - information very far from us becomes highly relevant to our survival as our body may approach it very soon). Furthermore, multiple studies show that the dorsal “where”/”how” pathway and the ventral “what” pathway are each sensitive to both “what” and “where” information. Incorporating findings from electrophysiological, neuropsychological, imaging, cytoarchitectural and behavioral investigations in primates and humans, here I propose that the visual system of the dynamically behaving human is composed of 3 main visual pathways, each revolving around a pivotal egocentric time range: NOW, SOON, and LATER. The “NOW” pathway (corresponding to motion-sensitive regions) processes all changes happening now across the visual field (predominantly visual motion), the “SOON” (dorsal) pathway processes all visual information

critical for immediately upcoming (≤3s) body-world interactions, and the "LATER" (ventral) pathway processes information that may be relevant later (>3s). Challenging the currently held view, this model predicts that each pathway is sensitive to what, where and who information according to its egocentric temporal relevance. This framework accounts for many inconsistent findings, predicts pathway-specific visual field, spatial and temporal sensitivities, and has implications to attention, consciousness, memory, and time.

Disclosures: S. Gilaie-Dotan: None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO41.05

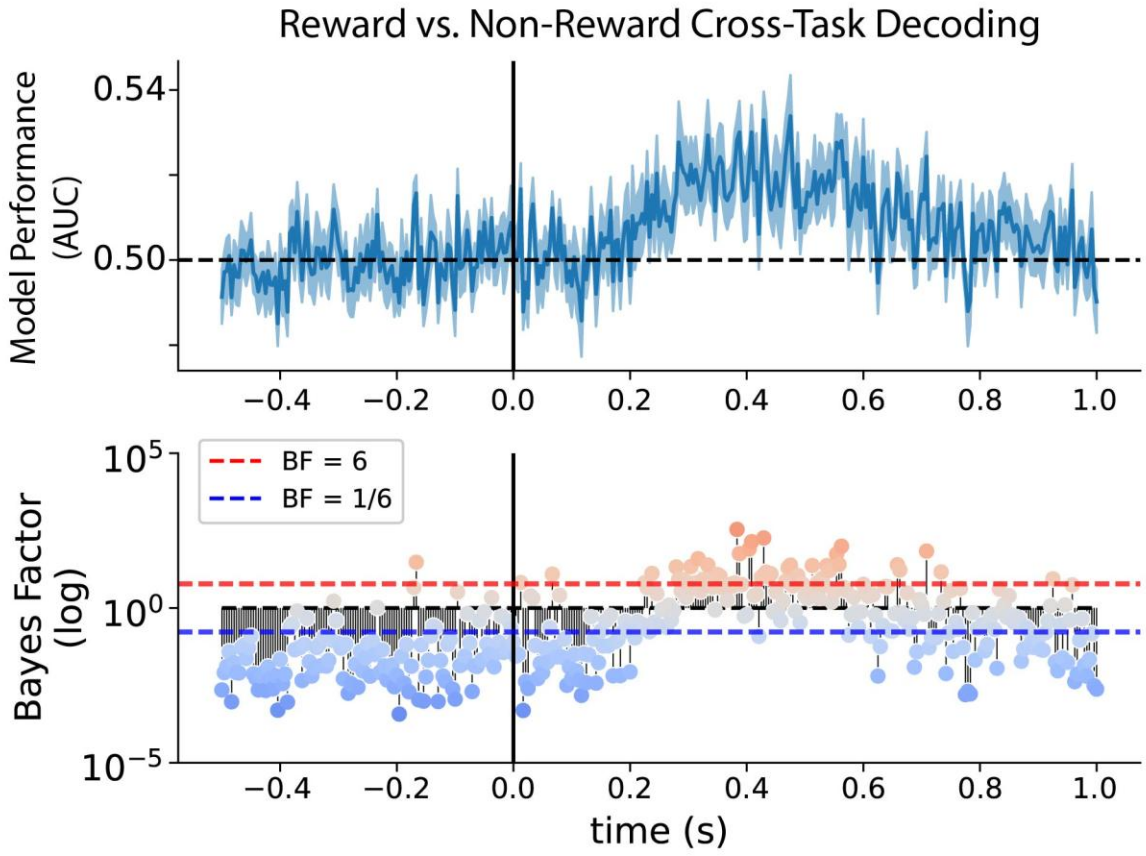
Topic: E.06. Vision

Support: ZIA MH002893

Title: Temporal dynamics of reward processing in visual decision-making

Authors: *C. J. H. PIRRUNG, D. ABDO KAHIN, C. I. BAKER;
Lab. Brain and Cognition, NIH, Bethesda, MD

Abstract: The Reward Positivity (RewP) is a sensitive EEG marker of reward receipt, that has been proposed as a candidate biomarker of Major Depressive Disorder (MDD). The RewP is likely generated by a distributed cortical network whose individual nodes contribute heterogenous information. Multivariate pattern analysis (MVPA) has shown increased sensitivity to neural signals and allowed for successful classification of perceptual stimuli based on evoked neural activity. Here we tested whether MVPA of MEG data can be used to temporally decode rewarding and non-rewarding feedback. Participants completed a visual (N=16) or auditory (N=16) reinforcement learning task, with 12 participants completing both. Color- and pitch-feedback mapping swapped on every run to maximally separate perceptual and cognitive elements of reward. Our sanity check models of color and pitch classification successfully predicted perceptual features. Decoding of feedback within each task revealed a sustained representation of reward. Cross decoding between tasks showed a similar representation. Sensor- and source-level searchlights revealed widespread distributions of decoding with peaks in sensory areas for auditory and visual features, as well as peaks in frontal areas (particularly anterior cingulate) for reward. These results suggest that MVPA can be used to effectively decode higher-order information beyond perception, even at the individual subject level. Additionally, our sensor and source searchlights suggest that reward is diffusely reflected in the brain, and that using ERP analyses may not capture the full breadth of this signal.



Disclosures: C.J.H. Pirrung: None. **D. Abdo Kahin:** None. **C.I. Baker:** None.

Nanosymposium

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Presentation Number: NANO41.06

Topic: E.06. Vision

Support: This work was supported by internal research funds from Georgetown University Medical Center to TTL.

Title: Improved blind field function with variable hMT+ engagement after neurorehabilitation in post-stroke visual field loss

Authors: *B. RISPOLI[1], K. MOON[1], S. MONTOYA[2], A. BIST[1], S. ABOOBUCKER SIDIQ[3], B. OSBORNE[4], T. T. LIU[1];
[1]Dept. of Neurol., Georgetown Univ., Washington, DC; [2]Dept. of Neurol., Georgetown Univ.,

Washington DC, DC; [3]Dept. of Neurol., Georgetown Univ., Washinton, DC; [4]Departments of Neurol. and Ophthalmology, Medstar Georgetown Univ. Hosp., Washington, DC

Abstract: Visual field loss is a common and disabling consequence of stroke, yet outcomes vary markedly across patients. While some report little to no awareness of stimuli in the blind field, others exhibit preserved motion, face, or object processing. This variability in residual visual abilities likely reflects individual differences in the structural and functional integrity of spared visual pathways, including subcortical projections to the human middle temporal complex (hMT+) that bypass damaged early visual cortex. As part of the VIBRANT (Vision Improvement through Behavioral Rehabilitation And Neuroplasticity Training) study, we assessed behavioral and neural changes following a structured neurorehabilitation intervention (transcranial electrical stimulation paired with motion-based perceptual learning) in four chronic stroke patients (3 male). Behavioral measures included an adapted clinical Humphrey Visual Field (HVF) 10-2 detection task and its two-alternative forced-choice (2AFC) version, a motion direction discrimination task, and a face and object categorization task. Eye-tracking confirmed stable central fixation and no systematic eye movements toward the blind field before or during peripheral stimuli (167 ms). Following intervention, all patients showed improved luminance detection within and near trained blind field locations as measured in the HVF detection task. Most also improved in motion direction discrimination, while gains in 2AFC detection and object/face categorization were more variable, suggesting partial generalization from motion-based perceptual learning to other visual domains. To examine the neural basis of these behavioral gains, participants completed hMT+ localizer and motion decoding fMRI tasks. The localizer assessed functional integrity of hMT+ in the lesioned hemisphere, while motion decoding examined whether multivoxel activity patterns in hMT+ distinguished motion direction in the blind field. Despite behavioral improvements, post-intervention changes in hMT+ decoding were heterogeneous across individuals. Whole-brain analyses revealed motion-related information decoding in alternative spared cortical regions in some patients, suggesting that recovery of blind field function may rely on distributed and individually specific neural architecture beyond canonical hMT+. These findings underscore the importance of neuroimaging-informed approaches to post-stroke visual rehabilitation.

Disclosures: B. Rispoli: None. **K. Moon:** None. **S. Montoya:** None. **A. Bist:** None. **S. Aboobucker Sidiq:** None. **B. Osborne:** None. **T.T. Liu:** None.

Nanosymposium

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Topic: E.06. Vision

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The Azrieli Foundation
The Research to Prevent Blindness Inc, NY
The Eye & Ear Foundation of Pittsburgh

Title: Machine learning segregates distinctive “Gaze-prints” between overlapping neurodevelopmental disorders

Authors: *I. AVNI[1], I. DINSTEIN[3], M. BEHRMANN[2];
[1]Ophthalmology, [2]Dept. of Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA; [3]Psychology, Ben Gurion Univ., Beer Sheva, Israel

Abstract: Although decades of research have sought distinctive phenotypes for segregating different neurodevelopmental disorders, a systematic set of features for the objective classification of these disorders has not been developed. Moreover, this effort is further challenged as several of the disorders have overlapping features. Here, we used gaze behavior, a ubiquitous, easily measurable behavior, coupled with machine learning (ML), to distinguish between three such disorders. We acquired detailed metrics of the gaze profile, or “Gaze-print”, of 96 participants diagnosed with Autism Spectrum Disorder (ASD), Epilepsy or Childhood Hemispherectomy (“Hemi”), and matched controls, all of whom viewed a short, engaging movie at least twice. We extracted 57 dependent measures that characterized properties of gaze: pupillary (e.g. mean change in pupil size), oculomotor (e.g. number of saccades), spatial (e.g. dwell time per location), perceptual (e.g. sensitivity to spatial frequency), social (e.g. percentage fixation on faces), and variability (inter- and intra-subject correlations over time). The univariate statistical analyses revealed a set of measures that differentiated between the Gaze-prints of the three disorder groups and their matched controls. In the multivariate analyses, a pairwise SVM classifier trained on all 57 features and, separately, on the top 3-feature subset (saccade distance ratio, horizontal distance from face Area Of Interest, and luminance) achieved mean classification accuracy of 86% and 84%, respectively, a compelling translational result. Together, these findings permit an understanding of the idiosyncratic phenotypes of different neurodevelopmental alterations and elucidate psychological and functional signatures that have potential diagnostic leverage.

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Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Presentation Number: NANO41.08

Topic: E.06. Vision

Title: Einstein’s brain: Analysis of the medial gyral anatomy reveals striking new structural anomalies

Authors: *C. W. TYLER;
Smith-Kettlewell Eye Res. Inst., San Francisco, CA

Abstract: Rationale. Einstein's brain has had a turbulent history and has been subject to a range of anatomical analyses, but the medial surface has been understudied. In view of his dominant role in the history of physics, it is of significant interest to assess his medial cortical topography.Methods. Although the brain has been sectioned in various ways, photographs of the intact brain were taken by pathologist Thomas Harvey in 1955 before sectioning it into 170 pieces. The photographs were published by Falk et al. (2013), who provide a qualitative analysis of the sulcal organization but do not comment on the posterior medial surface features, other than to say that the cuneus appears unusually convoluted. The present study focuses on quantifying the dimensions of the posterior medial gyri of Einstein's brain by measurements from the Harvey photographs, scaled in proportion to the standard Brodmann parcellation of the human brain. The medial surface is particularly suitable for this purpose since it is not subject to the projective distortion of photographic recordings of the curved surfaces of the rest of the brain.Results. The focus of the analysis is on the organization of the posterior medial cortex, which are associated with the capacity for visualization, spatial representation and navigational capabilities. Only significant results are quantified here. Remarkably, Einstein's calcarine sulci (V1) were only 78% of the length of the typical calcarine (BA 17), scaled as a proportion of his (typical) total brain length of 168 mm. The other occipital retinotopic areas were insufficiently definable for measurement. The posterior subdivisions of the precuneus area (BA 7pm) were 57% longer than their Brodmann template counterparts. The posterior cingulate cortex (PCC) regions accessible to quantification were BA 23 and 31. (The minor retrosplenial areas BA 26, 29, & 30 were not identifiable). The BA 23 were of typical length, whereas the anterior (a), posterior dorsal (pd) and posterior ventral (pv) subgyri of BA 31 were respectively 28%, 53% and 41% longer than their Brodmann template counterparts. Overall Einstein's precuneus/PCC areas had collectively about 60% greater areal ratio to V1 as the typical Brodmann organization. Conclusion. Several the identifiable gyri of the precuneus and PCC areas of Einstein's brain were significantly larger than the canonical Brodmann subdivisions (28-57%, relative to the typical coefficient of variation of ~10%). Overall, the precuneus/PCC cortex was 25% larger than its Brodmann template, implying an unusual extent of cortex devoted to egocentric spatial representation and mathematical reasoning.

Disclosures: C.W. Tyler: None.

Nanosymposium

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Presentation Number: NANO41.09

Topic: E.06. Vision

Support: NSF Grant 2547344
German Research Foundation (DFG) 556645169

Title: Linking category selectivity in high-level visual cortex and gaze behavior across development

Authors: ***M. LINKA**[1], E. IM[1], K. DUCRE[2], J. YAO[3], K. GRILL-SPECTOR[3];
[1]Stanford Univ., Stanford, CA; [2]Stanford Univ., Stanford,, CA; [3]Psychology, Stanford Univ., Stanford, CA

Abstract: Human high-level visual cortex contains clustered regions that respond more strongly to objects of ecologically prevalent categories, including faces, words, hands, and food than other stimuli. Across childhood development, neural selectivity in ventral temporal cortex (VTC) for faces and words increases, but neural selectivity in VTC for limbs decreases. However, it is unknown whether (1) these developmental changes are specific to VTC or if they extend to lateral occipitotemporal cortex (LOTC), and (2) whether they are linked to changes in children's visual diet. To address these questions, we measured neural responses in VTC and LOTC using fMRI and their gaze behavior outside the scanner using both fixed- and mobile eye tracking. During fMRI, 19 participants (ages 4-30) viewed images of faces, hands, words, objects, places, and food while performing a 1-back task. We determined in each participant the volume of category selectivity per category. During fixed-head eye tracking, 12 of the participants (ages 4-30) freely viewed a set of 40 scenes containing objects from the aforementioned categories. During mobile eye tracking, 8 of the participants (ages 4-17), performed everyday activities in their homes (in the wild) while their eye movements and visual scene were recorded. We determined the proportion of category-directed fixations to ecologically prevalent categories on images and in in the wild. We find age-related increases in word-selective activation in right VTC and bilateral LOTC as well as increases in face-selective activation in right VTC and left LOTC. In contrast, hand-selective activation decreases with age in left VTC, but not right VTC, and in right LOTC, but not left LOTC. Selectivity to instruments, food, and houses in VTC and LOTC did not change across age. Finally, we find that the volume of selective voxels was generally positively related to the proportion of fixations spent on the respective categories during both fixed and mobile eye tracking. Together, these results show developmental increases of face and word selectivity and decreases in hand selectivity in both VTC and LOTC and suggest that this development is coupled with changes in fixation behavior on these categories.

Disclosures: M. Linka: None. **E. Im:** None. **K. Ducre:** None. **J. Yao:** None. **K. Grill-Spector:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO41.10

Topic: E.06. Vision

Support: National Eye Institute RO1 EY030434
National Eye Institute RO1 EY0117081

NIH Shared Instrumentation Grant S10-RR019371
NIH Shared Instrumentation Grant P41-EB030006

Title: Differential impact of amblyopia on the contrast responses at different spatial frequencies in the magno- and parvo-cellular dominated columns of extrastriate cortex in humans

Authors: *A. B. MORLAND[1,2], J. SKERSWETAT[3,4], E. D. GAIER[5,6,8], P. BEX[4], D. HUNTER[5,6], S. NASR[2,7];
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Abstract: Amblyopia is characterized by a shift in ocular dominance that results from abnormal visual input affecting processing in the brain. We investigated how amblyopia impacts on mesoscale cortical sites that are selectively influenced by magno and parvocellular streams. We evaluated interocular differences in responses to sinusoidal gratings of different spatial frequency and contrast across color- and motion-selective columns in extrastriate visual areas, V2 and V3, at five log spaced spatial frequencies (0.1-5.8 c/deg). Measurements were made in 16 individuals with amblyopia and 8 individuals with typical vision under binocular and monocular conditions. Data were extracted for color- and motion-selective columns in central (0-3°) and peripheral (3-8°) representations of extrastriate cortical areas. While binocular responses, interestingly, were not different between groups, the difference between monocular responses of the dominant eye (DE) and non-dominant eye (NDE) varied by group. In amblyopia (but not controls), responses were greater for the DE. In the central representations, this preference was limited to low contrasts at high spatial frequency irrespective of the column type, demonstrating involvement of magno and parvocellular streams. In the peripheral representations, in the color-preferring columns preference for the DE was found at the same low contrasts at high spatial frequency, whereas in the motion preferring columns, the preference for the DE was far more widespread affecting all spatial frequencies and contrasts. In conclusion, this result provides the first direct evidence for a differential impact of amblyopia on the cortical columns in extrastriate cortex that are believed to preferentially receive magno- vs. parvocellular input. This finding supports previous reports from behavioral studies that amblyopia does not manifest solely as a parvocellular deficit and that a more general loss of function is characteristic of this developmental disorder.

Disclosures: A.B. Morland: None. **J. Skerswetat:** None. **E.D. Gaier:** None. **P. Bex:** None. **D. Hunter:** None. **S. Nasr:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

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Presentation Number: NANO41.12

Topic: E.06. Vision

Support: Neukom Institute for Computational Sciences
Brain and Behavior Research Foundation

Title: Beyond reinstatement: Distinct cortical activity for perception, imagery, and episodic projection

Authors: *A. D. STEEL[1], P. A. ANGELI[2], L. M. DINICOLA[3];
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Abstract: When we remember the past or plan for the future, we mentally simulate the experience, a process called episodic projection. Current reinstatement models predict this process recruits the same sensory brain areas supporting ongoing perception. Here, we asked whether scene perception, mental imagery, and episodic projection share a common cortical locus, or are instead organized along a functional hierarchy. We compared activity locations across two fMRI datasets in which individual participants performed scene perception and mental imagery of scenes (n=12) or episodic projection (n=15). In Dataset 1, participants passively viewed scene images or mentally recalled personally familiar locations, cued by place names (adapted from Steel et al., 2021); resting-state fMRI was also acquired. In Dataset 2, participants read scenario statements about their own past or future personal experiences and selected from multiple-choice answers, contrasted with questions probing their present mental state (DiNicola et al., 2020). When activity was projected into a shared stereotaxic space, these tasks revealed anatomically distinct activity clusters progressing anteriorly across lateral parietal cortex, suggesting a possible hierarchical organization. Scene perception drove activity in posterior unimodal retinotopic cortex; mental imagery evoked activity at the inflection point between unimodal and transmodal cortex; and episodic projection drove activity anterior to imagery, largely within transmodal cortex. Resting-state fMRI further showed that hippocampal connectivity peaked within the episodic projection cluster, anterior to the imagery cluster, suggesting the hippocampus preferentially interfaces with the most transmodal stage of this cortical hierarchy. We also observed repetition of this topographic organization (perception-imagery-projection) within ventral, medial, and prefrontal cortices, suggesting a broader organizational principle. These results challenge pure reinstatement accounts of episodic memory recall, instead suggesting that scene perception, mental imagery, and episodic projection engage distinct, hierarchically organized brain regions. This architecture may reflect a neural mechanism for progressively transforming information from the immediate visual scene, to memory-based scene representations, to the temporally situated events of episodic projection.

Disclosures: A.D. Steel: None. **P.A. Angeli:** None. **L.M. DiNicola:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO41.13

Topic: E.06. Vision

Support: NIH Grant R01 EY025670
NIH Grant R01 NS123778

Title: Monkey business in human development: shared gaze biases in natural scene viewing across species and age

Authors: *S. SHARMA[1], M. LINKA[2], M. BRODA[3], B. DE HAAS[3], M. S. LIVINGSTONE[1]; [1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Psychology, Stanford Univ., Stanford, CA; [3]Allgemeine Psychologie, Justus Liebig Univ., Giessen, Germany

Abstract: Visual exploration of natural scenes in humans can be better predicted by high-level semantic content than by low-level saliency alone, but gaze biases also vary substantially across development. This raises the question of which gaze biases reflect conserved primate characteristics, and which are human-specific. Here, we analyzed free-viewing behavior of 8 macaques (age = 9.13 ± 5.1 years) across 200 natural scenes. We compared these data with existing human datasets, including 103 adults (age = 25.17 ± 5.5 years; Linka & de Haas, 2020) viewing the same 200 images and a large developmental sample of more than 6000 participants (ages 5-55 years) viewing a 40-image subset (Linka et al, 2025). Adult humans and monkeys showed broadly similar oculomotor behavior, including comparable fixation numbers, fixation durations, saccade amplitudes, and center-biased viewing. They also showed similar viewing patterns across images with high monkey-human fixation heatmap correlations that were not fully explained by low-level saliency. When we extended the comparison across development, we found that monkey-human similarity followed an age-related gradient: monkey scene viewing was more similar to young children than adults, a pattern that was only partly explained by text-directed gaze and not reducible to low-level saliency. A time-resolved analysis using 200-ms bins further showed that monkey-human gaze alignment peaked early after image onset across all age groups but remained higher for younger children than adults across most of the viewing period. Together, these results indicate that natural scene viewing is strongly shared across primates, but that human gaze becomes increasingly specialized with age. Macaque viewing may therefore reveal conserved foundations of primate attention, while developmental changes in humans add cultural biases that account for part of the remaining divergence.

Disclosures: S. Sharma: None. **M. Linka:** None. **M. Broda:** None. **B. de Haas:** None. **M.S. Livingstone:** None.

Nanosymposium

NANO41: Visual Cortex: Functional Architecture and Circuits

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO41.14

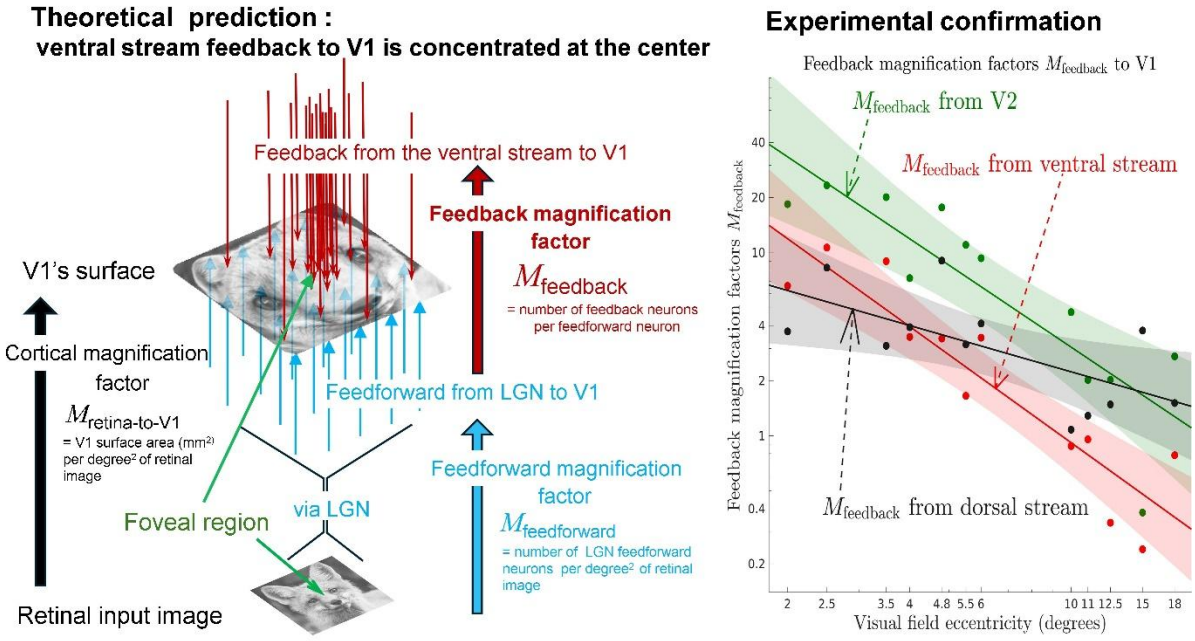
Topic: E.06. Vision

Support: Funding from the University of Tübingen and the Max Planck Society to Li Zhaoping
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Australian Research Council: DP250101768 to MGP Rosa

Title: Magnification of the central visual field by ventral stream feedback to primary visual cortex (V1) in primates: confirmation of a theoretical prediction

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Abstract: V1 allocates a larger cortical magnification factor to the central than the peripheral visual field. Meanwhile, many V1 neural properties, such as cell densities and neural connectivity, are approximately uniform across the V1 surface. Here we report a striking decline in the density of feedback projections from the ventral visual stream to V1 with increasing visual-field eccentricity in marmosets, as predicted by the Central-Peripheral Dichotomy (CPD) theory. We injected retrograde tracers into twelve V1 sites representing eccentricities from 2° to 18°. For each injection, we quantified the numbers of tracer-labelled neurons in each cortical area outside V1 and in the feedforward lateral geniculate nucleus (LGN). For each cortical area, the ratio of the numbers of cortical to LGN labelled neurons quantified the feedback magnification factor, $M_{feedback}$, defined as the number of feedback neurons per feedforward neuron projecting to a given V1 patch. $M_{feedback}$ decreased by an order of magnitude with increasing eccentricity for V2 feedback and for feedback pooled across ventral-stream areas, whereas the decrease was less steep for feedback pooled across dorsal-stream areas.
The CPD theory was motivated by the attentional bottleneck that allows only a tiny fraction of visual inputs to be recognized. It proposes that vision in the peripheral visual field specializes in selecting this fraction, mainly by gaze shifts to center the selected content at fovea, whereas vision in the central visual field specializes in recognizing the selected content. Assuming that the bottleneck starts from V1 to downstream areas, the theory further proposes that, during ongoing recognition, downstream areas send feedback to query for additional information that can disambiguate between competing perceptual hypotheses. Hence, it hypothesizes that the feedback to upstream areas, particularly V1, is concentrated on central-field representations. Since the ventral stream is mainly for recognition, a strong central bias in ventral-stream feedback to V1 is predicted and is confirmed by our findings.



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Nanosymposium

NANO42: Sleep Systems in Health and Disease

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Time: Wednesday, November 18, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO42.01

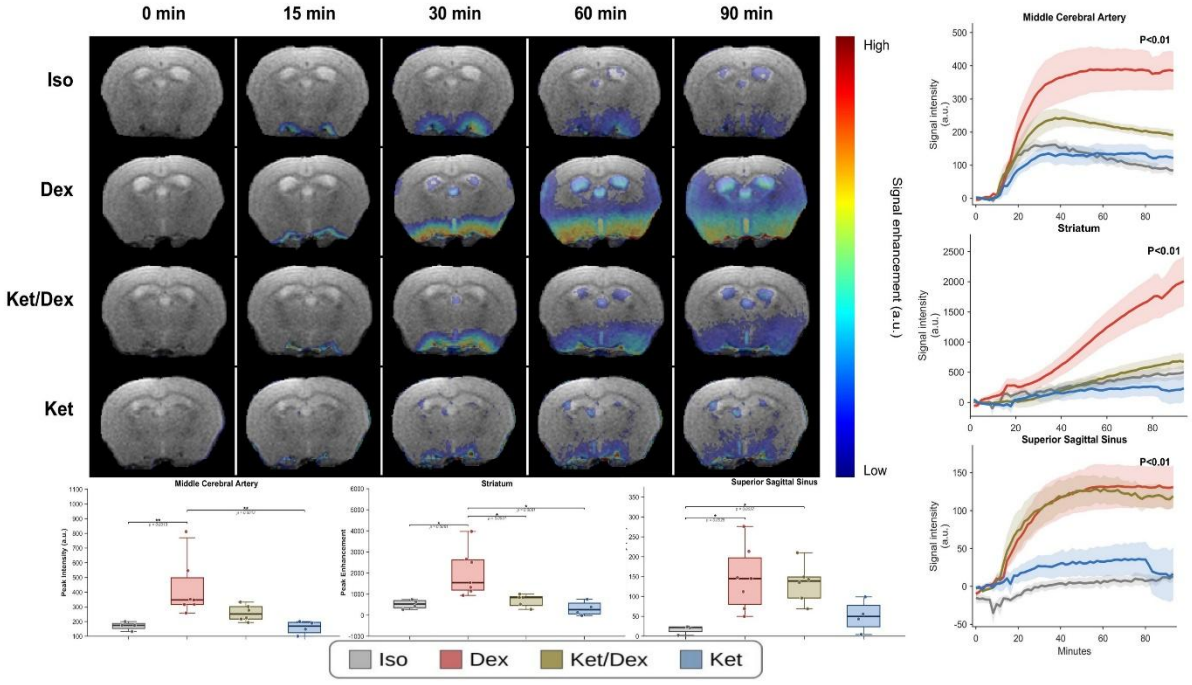
Topic: G.07. Biological Rhythms and Sleep

Title: Sleeping Beauty: How Sedatives and Anesthetics Shape Glymphatic Function

Authors: A. ALGANTIRY[1], C. STINE[2], R. N. AHMAD[3], J. MUNSON[2], *J. L. LECLERC[1]; [1]Univ. of Virginia, Charlottesville, VA; [2]Fralin Biomed. Res. Inst. at Virginia Tech. Carilion, Roanoke, VA; [3]Fralin Biomed. Res. Inst. at Virginia Tech. Carilion,, Roanoke, VA

Abstract: Introduction The glymphatic system is a brain-wide clearance pathway responsible for removing metabolic waste products and toxins, functioning primarily during sleep. Anesthetics and sedatives produce varying effects on EEG activity and delta power and have been shown to alter glymphatic function. However, agent-specific effects remain unknown, as prior studies relied on drug combinations and agents with limited clinical relevance. **Methods** Male C57BL/6 mice (8-12 wk, n=4-8/group) underwent cisterna magna cannulation, then 9.4T dynamic contrast-enhanced MRI (DCE-MRI) under dexmedetomidine, isoflurane, ketamine, or ketamine-dexmedetomidine anesthesia. Tracer was tracked over 90 min across 15 volumes of interest spanning influx, parenchymal, and clearance compartments plus whole brain. Comparisons used Kruskal-Wallis with Dunn's post-hoc test.**Results** Dexmedetomidine

consistently produced the greatest enhancement, followed by ketamine-dexmedetomidine, ketamine, and isoflurane. At CSF entry sites it drove the highest influx along all major arteries (basilar, Circle of Willis, MCA, basal foramina; P<0.05), and dominated intraparenchymal exchange across cortex, hippocampus, hypothalamus, striatum, and thalamus, (P<0.05). Clearance, however, was route-selective: enhancement was significant only at the olfactory bulb and superior sagittal sinus (P<0.01), with no differences along nasal turbinate, pharyngeal lymphatic, or cranial nerve routes. **Conclusion** Anesthetic and sedative choice shapes glymphatic influx and parenchymal exchange brain-wide while enhancing clearance route-selectively, scaling with how closely the brain state resembles natural sleep and peaking under dexmedetomidine's NREM-like profile. These findings inform operating-room and ICU management of patients at risk for postoperative delirium and cognitive impairment.



Disclosures: A. Algantiry: None. **C. Stine:** None. **R.N. Ahmad:** None. **J. Munson:** None. **J.L. Leclerc:** None.

Nanosymposium

NANO42: Sleep Systems in Health and Disease

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO42.02

Topic: G.07. Biological Rhythms and Sleep

Support: TriService Nursing Research Program (TSNRP)

Title: Detection of Slow-Wave Sleep in Wearable Capacitance-Based Intracranial Pressure Signals

Authors: *J.-H. CHUNG[1], C. LEE[2], S. KIM[2], K. H. CHOI[3], V. SAKTHIVELPATHI[4], A. DEOLE[2];
[1]Mechanical Engin., [2]Univ. of Washington, Seattle, WA; [3]Psychiatry, Uniformed Services Univ., Bethesda, MD; [4]Nanosync Labs, Redmond, WA

Abstract: The glymphatic system clears metabolic waste from the brain during sleep, with slow-wave sleep (SWS) playing a critical role. While polysomnography (PSG) measures neural and physiological activity, it does not provide a direct view of brain fluid dynamics. Intracranial pressure (ICP), which is influenced by cerebral blood flow, cerebrospinal fluid circulation, and sleep-state transitions, may offer complementary information about these processes. We hypothesized that capacitive sensors integrated into a wearable sleep mask, designed to measure regional ICP, could detect spectral signatures associated with SWS. Six healthy adults (20-60 years old) wore the sleep mask for two consecutive nights, yielding 12 recordings. From the capacitance signal, we extracted mean values along with respiratory (RS) and heartbeat (HB) components and compared them with PSG-derived respiratory flow, ECG, and photoplethysmography (PPG). Following per-session calibration, HB rate estimation achieved a mean absolute error of 4.19 BPM, representing a 77% reduction from the uncalibrated baseline. RS accuracy improved by approximately 25%. Calibration scaling factors remained stable within individuals across nights but varied with SWS, suggesting that autonomic activity modulates the capacitance signal. To identify SWS-related features, we applied spectral ridge tracking to time-frequency signals. This method detected persistent narrow-band peaks in the spectrogram and linked them over time into continuous ridges within the 0.1-5 Hz frequency range. Non-sinusoidal oscillations generated harmonic ladders consisting of a fundamental frequency and its integer multiples, which appear as co-occurring ridges at harmonic ratios. Among motion-artifact-free epochs, 58% contained harmonically related spectral peaks, and 44% exhibited persistent ridges. Individual ridges lasted as long as 74 minutes, with a median session maximum of 25 minutes. During PSG-confirmed N3 sleep, ridge power decreased by approximately 40% compared with other sleep stages, and fewer harmonic groups were active. These findings were consistent with the slower and more regular oscillations in deep sleep. Together, these results demonstrated that the capacitance signals contained structured spectral features that distinguished SWS. A wearable sleep mask based on this approach could provide a practical, noninvasive method for detecting deep sleep and, potentially, monitoring glymphatic-related physiology outside the sleep laboratory.

Disclosures: J. Chung: None. **C. Lee:** None. **S. Kim:** None. **K.H. Choi:** None. **V. Sakthivelpathi:** None. **A. Deole:** None.

Nanosymposium

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Topic: G.07. Biological Rhythms and Sleep

Support: SSTF SSTF-BA2402-05
NRF RS-2024-00345236
NFEC RS-2024-00401876
NRF 2019R1A6A1A10073887

Title: Conserved Dream-Related Cortical Dynamics of PGO/P-Wave Activity Across Species

Authors: *J. KIM[1], K. PARASHAR[1], J. LEE[1], I. JOO[1], C. CHUNG[2], K.-Y. JUNG[3];
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Abstract: Ponto-geniculo-occipital (PGO) waves in primates and their rodent homologues, P-waves, are phasic sleep events strongly associated with REM sleep and dreaming. Although their pontine origins and possible thalamocortical pathways have been described, how PGO/P-waves are expressed in cortical activity across sleep stages and whether these cortical signatures are conserved across species remain unclear. Here, we characterized PGO/P-wave-related cortical dynamics across rats, macaque monkeys, and humans. In rats, we recorded pontine activity from the subcoeruleus nucleus together with cortical and parietal EEG/LFP signals during natural sleep. In macaques, we analyzed publicly available high-density ECoG recordings from two animals obtained from Neurotycho.org, using a 128-channel array covering one cortical hemisphere. In humans, we analyzed intracranial ECoG recordings and scalp EEG with full polysomnography during natural sleep. Across species and recording modalities, PGO/P-wave-related events showed consistent coupling with cortical theta oscillations. Notably, these events exhibited robust phase locking with frontal theta activity, suggesting that coordination between pontine phasic events and frontal cortical theta dynamics is a conserved feature of sleep. In macaques, waveform-based analyses with high-density cortical recordings further revealed spatially isolated and region-specific PGO-wave-related cortical profiles across anatomical areas, indicating that PGO/P-wave-related activity is expressed through localized rather than globally uniform cortical dynamics. Importantly, we also detected PGO-wave-related signatures in human scalp EEG using occipital EEG-based detection, supporting the feasibility of identifying these events from non-invasive cortical recordings. Together, these findings demonstrate conserved, state-dependent coordination between PGO/P-wave-related events and cortical theta dynamics across rodents, non-human primates, and humans, and provide a cross-species foundation for studying sleep- and dream-related neural activity from cortical recordings alone.

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Nanosymposium

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Presentation Number: NANO42.04

Topic: G.07. Biological Rhythms and Sleep

Support: NSTC 114-2221-E-007 -128 -MY3

Title: In-Ear EEG Device for Precise Sleep Monitoring in Ambulatory Settings

Authors: T.-Y. YEN[1], J. LIN[2], Y. WENG[3], ***H. CHEN**[4];
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[3]BioPro Scientifics, Hsinchu, Taiwan; [4]Natl. Tsing Hua Univ., HsinChu, Taiwan

Abstract: Background: Physiological signals such as those from electroencephalography (EEG) and photo-plethysmography (PPG)are essential for monitoring neurological activity and vital signs. While PPG devices integrated into wearables like smartwatchesprovide basic health insights, they often fail to meet clinical standards for applications such as sleep stage analysis. Conversely,clinical-grade devices, though comprehensive, are mostly restricted to professional settings, limiting their utility for continuoushealth monitoring.Objective: To overcome these limitations, BioPro Scientific has developed an ambulatory EEG/PPG device suitable for homeuse, combining the convenience of wearable technology with the detailed analytics typically reserved for clinical environments.
Methods: This device was rigorously tested in a collaborative study with the sleep lab at National Cheng-Chi University,comparing its performance against standard polysomnography (PSG). Key metrics such as correlation, coherence, and sleepstaging were evaluated to assess the device's efficacy.
Results: The ambulatory EEG/PPG device demonstrated a high correlation with PSG standards, indicating its capability toreliably monitor sleep stages. Initial U-sleep model testing for ear EEG data achieved an accuracy of 78%. To enhance this, wedeveloped specialized de-noise and sleep staging AI models using open-source datasets, achieving over 95% efficiency in noisereduction and an accuracy of over 80% in sleep staging.
Conclusions: The promising results indicate that our device can significantly improve home-based health monitoring andwellness strategies by enabling accurate longitudinal sleep analysis in natural settings. Ongoing refinements, particularlythrough fine-tuning the AI models with ear EEG data, are expected to further enhance its performance, paving the way forwidespread adoption of ambulatory EEG technology for reliable automatic sleep analysis.

Disclosures: T. Yen: A. Employment/Salary (full or part-time):; BioPro Scientific Co., Ltd.. **J. Lin:** None. **Y. weng:** A. Employment/Salary (full or part-time):; BioPro Scientific Co., Ltd. **H. Chen:** A. Employment/Salary (full or part-time):; BioPro Scientific Co., Ltd..

Nanosymposium

NANO42: Sleep Systems in Health and Disease

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO42.05

Topic: G.07. Biological Rhythms and Sleep

Support: NIH grants P41-EB015896, R21-NS106706, R01-EB019437, P41- EB030006, R00-MH111748, R01-AG070135, S10-OD023637 and S10-RR019371

Title: Brainstem control of cerebrospinal fluid dynamics during sleep

Authors: *D. CHEN[1], N. CICERO[2], L. D. LEWIS[1];
[1]MIT, Cambridge, MA; [2]Boston Univ. / MIT, Somerville, MA

Abstract: Brain fluid transport has been hypothesized as a key component of the brain's clearance system, but the neural mechanisms driving cerebrospinal fluid (CSF) movement remain poorly understood. In humans, large waves of CSF flow through the fourth ventricle appear during non-rapid eye movement (NREM) sleep, and these CSF waves are coupled to large-scale cortical hemodynamic oscillations, which are thought to drive CSF movement through blood volume changes via neurovascular coupling. However, the upstream neural drivers of this cortical-CSF coupling remain unknown. Brainstem nuclei, such as locus coeruleus (LC), modulate arousal state, vascular tone, and global neural activity, positioning them as candidate regulators of sleep-dependent CSF dynamics. Here, we investigated whether activity across a specific set of subcortical arousal nuclei is linked to CSF flow during sleep. We acquired simultaneous EEG-fMRI data at night while participants spontaneously transitioned between sleep-wake states, using a brainstem-optimized acquisition (7 Tesla MRI; 1.2mm isotropic voxels; TR=0.98s; N=17 scanning sessions), with participants instructed to press a button approximately every second while awake. We analyzed activity in LC and other subcortical arousal nuclei, locked to peaks in fourth-ventricle CSF flow during sleep. We found that LC activity showed significant changes in activity 16s before CSF flow, and was strongly coupled to CSF flow during NREM ($r = 0.87$). Notably, LC signal changes also preceded cardiac amplitude changes (-11s relative to CSF peak) and cortical BOLD changes (-7s), consistent with its involvement in regulating neurovascular changes that drive CSF displacement. Similar early activity was observed in other subcortical nuclei, including basal forebrain (-18s; $r=0.90$), median raphe (-17s; $r=0.85$), thalamus (-15s; $r=0.87$), and periaqueductal gray (-14s; $r=0.97$), suggesting that CSF regulation might be a function of the broader subcortical arousal system across several neuromodulatory regions. Behavioral arousal state, indexed by button-press frequency, also showed a significant decline followed by an increase that peaked at the time of CSF flow, indicating arousal state fluctuations. These results place brainstem activity at the start of a structured neural-autonomic-vascular cascade in which arousal level, cortical hemodynamics, and CSF flow might be co-regulated by subcortical neuromodulatory processes. This finding reframes sleep-dependent CSF flow as a circuit-level output of brainstem arousal control, with potential implications for brain clearance during sleep.

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Nanosymposium

NANO42: Sleep Systems in Health and Disease

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 8:00 AM - 11:15 AM

Presentation Number: NANO42.06

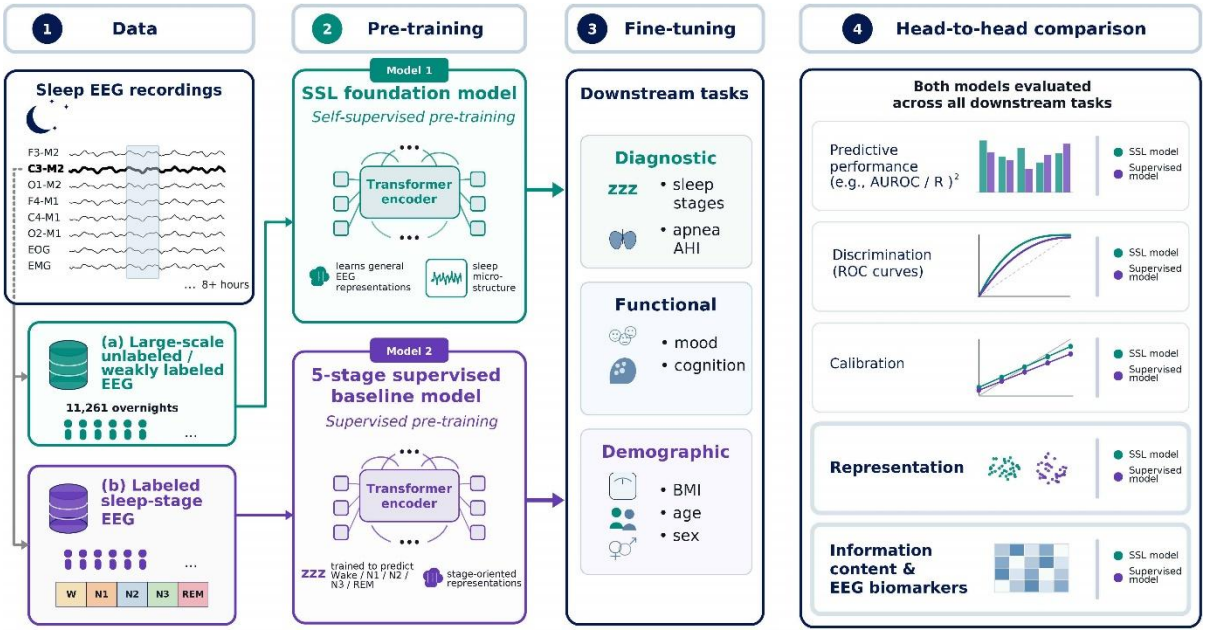
Topic: G.07. Biological Rhythms and Sleep

Support: APL Research and Exploratory Development Department (REDD) Independent Research and Development (IRAD)

Title: Sleep EEG foundation models reveal within-stage microstructure that improves health screening beyond traditional stages

Authors: ***W. G. COON**, M. OGG;
Johns Hopkins Univ. Applied Physics Lab., Laurel, MD

Abstract: Sleep physiology provides rich longitudinal biosignals reflecting integrated brain and systemic physiology, yet polysomnography is commonly compressed into coarse, human-defined stages. We asked whether self-supervised foundation models learn sleep EEG structure beyond traditional staging and encode enriched health information. Using 11,261 overnight recordings, we trained transformers on unlabeled sleep data and probed representations across diagnostic, demographic and functional outcomes. Compared with architecture-matched transformers trained from random initialization on each downstream task, SSL pretraining improved performance across several outcomes. Compared with five-stage-supervised pretraining, EEG-only advantages were clearest for BMI and age, while differences for AHI, sex, and functional outcomes were smaller, nominal, or not reliable. In nested controls, EEG-derived self-supervised model scores retained incremental value beyond covariates, stage summaries, spectral summaries, and a matched five-stage representation. Embedding analyses show that models recover the stage scaffold without labels while preserving higher-resolution, stage-anchored structure that carries task-specific health information beyond the five-stage interface



Disclosures: W.G. Coon: None. **M. Ogg:** None.

Nanosymposium

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Presentation Number: NANO42.07

Topic: G.07. Biological Rhythms and Sleep

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the Simons Foundation Collaboration on Plasticity in the Aging Brain (#811231)
National Institutes of Health awards R01-AG070135
U19-NS128613, the Corundum Convergence Institute
MIT Artificial Intelligence and Wellness Fellowship

Title: Closed-loop Auditory Stimulation during Sleep Acts as Pacemaker to Tighten Fronto-limbic Coupling and Enhance Cerebrospinal Fluid flow in Young and Aging Humans

Authors: *X. ZENG[1], J. LEVITT[3], L. D. LEWIS[2];
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Abstract: The brain relies on sleep-dependent cerebrospinal fluid (CSF) pulsatility to clear toxic metabolic waste, a process critical for preventing neurodegeneration. This key process of CSF flow during non-rapid eye movement (NREM) sleep is driven by cascade of neural slow waves (SWs) and hemodynamic fluctuations. A recent proof of concept study in young adults showed that closed-loop auditory stimulation (CLAS) enhances EEG slow waves and CSF pulsatile flow. However, its deep-brain mechanisms and translatability to aging brains—where clearance is most essential—are not yet understood. To determine exactly how CLAS mechanistically drives network synchronization and downstream CSF pulsatility, we deployed a real-time phase-locked CLAS algorithm during simultaneous EEG-fMRI NREM sleep in young adults (n=14, age 18-60 years) and an older cohort (n=7, age 60-80 years). Using single-trial linear mixed-effects (LME) modeling on EEG, Blood Oxygenation Level Dependent (BOLD) fMRI signals, and CSF flow timeseries, we mapped the spatiotemporal propagation of BOLD signals and deep-brain functional connectivity change after stimulation delivery. In young adults, we found that CLAS acts as a biomimetic network amplifier that engages same set of brain circuitry as spontaneous SWs. The acoustic stimulus successfully bypasses conscious lemniscal pathways—evoking no primary auditory cortex activation—and routes directly to the frontal lobe. There, it acts as a temporal pacemaker, accelerating fronto-limbic synchronization and forcing the cortex, specifically the vmPFC, into an amplified negative BOLD down-state. This artificially deepened cortical down-state acts as a vascular vacuum, driving a significantly larger pulsatile inflow of cleansing CSF compared to spontaneous sleep. However, preliminary analyses in our aging dataset reveal significant biophysical bottlenecks to this mechanistic pathway. When compared to the young cohort via combined interaction models, older brains exhibited a trend of degraded baseline thalamocortical connectivity, which correlated with lower response to the auditory tone. Furthermore, older subjects demonstrated lower BOLD-CSF coupling, consequently dampening the downstream fluidic wash even when slow waves were successfully amplified. These simultaneous EEG-fMRI findings establish CLAS as a pacemaker for driving glymphatic

pulsatility, while highlighting that future non-invasive therapeutics must adapt to overcome age-related network and vascular decoupling.

Disclosures: X. Zeng: None. **J. Levitt:** A. Employment/Salary (full or part-time):; Co-founder Cerebloom;. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patent application. **L.D. Lewis:** A. Employment/Salary (full or part-time):; Co-founder Cerebloom. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on patent application.

Nanosymposium

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Topic: G.07. Biological Rhythms and Sleep

Support: Institutional and Foundational Support

Title: AI-Guided Closed-Loop Auditory Stimulation Reveals a Recoverable Post-Apnea Thalamocortical State

Authors: J. JORDAN-FANCHER[1], *F. JEFFERSON[2];
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Abstract: Obstructive sleep apnea (OSA) disrupts sleep through repeated respiratory events that fragment thalamocortical activity. Although airflow is restored following apnea termination, neural recovery may lag behind physiological recovery, creating a transient state characterized by spindle suppression, elevated cortical activation, and reduced oscillatory stability. The neurophysiological properties of this post-apnea recovery state remain poorly understood. We propose that targeted auditory stimulation delivered immediately following apnea-related arousals can accelerate restoration of sleep-associated thalamocortical rhythms. Participants underwent overnight polysomnography with continuous EEG, respiratory, and oxygen-saturation monitoring. Machine-learning models trained using large-scale sleep resource databases identified post-apnea recovery windows in real time as opportunities for personalized low-frequency auditory stimulation. Neural recovery is quantified using period-amplitude analysis, spindle dynamics, spectral power distributions, and oscillatory stability metrics. We hypothesize that post-apnea recovery constitutes a distinct and measurable neural state and that closed-loop stimulation will promote faster re-establishment of sleep spindles and slow-wave activity while reducing wake-associated beta activity. AI-based analytical frameworks incorporating privacy-preserving synthetic sleep data will be used to improve model robustness and representation across populations. By targeting neural recovery rather than respiratory cessation, this work introduces a new framework for investigating thalamocortical resilience in sleep-disordered

breathing and establishes a foundation for adaptive neural technologies designed to restore healthy sleep network dynamics.

Disclosures: J. Jordan-Fancher: None. **F. Jefferson:** A. Employment/Salary (full or part-time):; North Carolina A & T State University.

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Title: Neocortical long-range inhibition promotes cortical synchrony and sleep

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Abstract: Sleep and wakefulness are associated with distinct cortical patterns of rhythmic activity. During low-arousal states such as slow wave sleep, synchronous low-frequency rhythms dominate activity across widespread cortical regions. Although inhibitory neurons are increasingly recognized as key players of cortical state, the *in vivo* circuit mechanisms coordinating synchronized activity across local and distant neocortical networks remain poorly understood. Here, we show that somatostatin and chondrolectin co-expressing cells (Sst-Chodl), a sparse and genetically distinct class of neocortical GABAergic inhibitory neurons, are selectively active during low-arousal states and largely silent during periods of high arousal. In contrast to most neocortical inhibitory neurons, Sst-Chodl cells, despite being extremely sparse, exert widespread influence across the neocortex via long-range axons that simultaneously target multiple regions. Selective activation of Sst-Chodl cells is sufficient to promote multi-region cortical synchronization characteristic of low-arousal states and to induce sleep. Together, these findings show that long-range Sst-Chodl inhibitory neurons not only track behavioral state but can actively promote sleep-like cortical activity and sleep behavior, highlighting an important contribution of cortical circuits to sleep regulation alongside established subcortical mechanisms.

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Presentation Number: NANO42.10

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant EY034617

Title: State-Dependent VIP Interneuron Dynamics in Developing Cortical Circuits

Authors: *J. BARNETT[1], G. MATTESSICH[2], R. BATISTA-BRITO[3];
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Abstract: The first two postnatal weeks in mice represent a critical period for cortical circuit assembly, corresponding roughly to the last trimester of human pregnancy, a highly sensitive window for neurodevelopmental disorders. Inhibitory interneurons play a central role in shaping these emerging circuits. Among them, vasoactive intestinal peptide-expressing interneurons

(VIP-INs) are uniquely positioned to regulate network maturation by modulating local circuit activity and coordinating state-dependent dynamics.
During early development, cortical activity transitions from spontaneous, highly synchronous patterns, such as retinal wave-driven activity in visual cortex, to more mature, behaviorally coupled population dynamics. This shift coincides with key developmental milestones, including eye opening, the onset of active sensing, and the emergence of structured arousal states, including sleep and wake. However, how VIP-IN activity evolves across this transition, and how it relates to emerging behavioral and state dynamics, remains poorly understood.
Here, we use in-vivo calcium imaging in primary visual cortex (V1) to track VIP-IN activity across early postnatal weeks, revealing a progressive increase in state-dependent modulation. We examine how VIP-IN activity changes across developmental stages and behavioral states, with a focus on the transition at eye opening and the onset of active sensing.
By linking VIP-IN activity to state-dependent dynamics and sensory engagement, this work aims to define how VIP-INs contribute to the emergence of functional neocortical networks. Disruptions in these processes may provide a mechanistic link between interneuron dysfunction and altered state regulation in neurodevelopmental disorders.

Disclosures: J. Barnett: None. **G. Mattessich:** None. **R. Batista-Brito:** None.

Nanosymposium

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Presentation Number: NANO42.11

Topic: G.07. Biological Rhythms and Sleep

Title: An SFO-MnPO Circuit Senses Osmotic Shifts to Gate Sleep Continuity

Authors: *W. ZHANG, B. HE, X. ZHANG;
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Abstract: Systemic osmolality fluctuates to maintain internal homeostasis, however, how interoceptive circuits encode these physiological signals to modulate sleep continuity remains poorly understood. Here, we demonstrate that a subfornical organ to median preoptic nucleus (SFO-MnPO) pathway that regulates sleep continuity in response to osmotic shifts. In vivo fiber photometry in $VGLUT2^{Cre}$ mice (8 weeks old, n = 6) revealed that SFO^{Vglut2} calcium transients actively track sleep-wake transitions, elevating prominently during spontaneous microarousals (MAs) and wake episodes. Under physiological conditions, delivering graded hypertonic saline challenges directly promoted instant awakenings and disrupted sleep architecture. This phenotype was fully recapitulated by optogenetic activation of SFO^{Vglut2} neurons at either the somata or their MnPO axon terminals, as well as by chemogenetic overactivation of this circuit, confirming that this system natively senses osmotic status to tune sleep stability. To determine how this osmosensitive mechanism is pathologically co-opted under chronic osmotic distress, we

utilized a model of chronic kidney disease (CKD) in male Vglut2^{cre} mice (n = 10), in which analysis revealed severe sleep quality impairment in CKD mice, marked by increased MAs, fragmented sleep, and a profound escalation in sleep state transition frequencies. Furthermore, we found that CKD mice increased approximately 25% (mean 24.8% SEM6.9) of sound-evoked awakenings (SEAs) compared to normal mice (n = 4), which rendered significantly more susceptible to external acoustic disturbances. Concurrently, fiber photometry revealed that during this pathological state, SFO^{Vglut2} neurons are abnormally hyperactivated, displaying a significant increase in calcium transients per hour during NREM sleep (n = 5). Crucially, circuit-specific chemogenetic inhibition of SFO^{Vglut2} neurons significantly decreased abnormal sleep state transitions and lowered MA frequency, successfully rescuing sleep fragmentation in CKD mice (Two-way ANOVA, $p < 0.05$, n = 10). Together, our findings identify the SFO-MnPO pathway as an osmosensitive circuit that gates sleep continuity in physiology and demonstrate that its pathological hyperactivation drives severe sleep disturbances during chronic kidney disease.

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Presentation Number: NANO42.12

Topic: G.07. Biological Rhythms and Sleep

Support: ZIA AA000416

Title: Behavioral Tolerance Following Chronic Vaporized THC Exposure: Implications for Sleep Dysregulation and TRN CB1R Signaling

Authors: *S. KANJANDA[1], R. PAWLOSKY[2], M. PAVA[3], A. KESNER[4], D. LOVINGER[2]; [1]Natl. Inst. on Alcohol Abuse and Alcoholism (NIAAA), Arlington, VA; [2]Natl. Inst. on Alcohol Abuse and Alcoholism (NIAAA), Rockville, MD; [3]Biol. Technologies Office, Def. Advanced Res. Projects Agency, Arlington, VA; [4]Indiana Univ. - Sch. Of Sci., Indianapolis, IN

Abstract: Sleep disturbance is a hallmark symptom of cannabis withdrawal, yet the neural adaptations underlying these effects remain poorly understood. Sleep spindles are oscillatory events that support sleep stability and memory consolidation and are generated by thalamic reticular nucleus (TRN)-thalamocortical circuits. The TRN expresses a high density of cannabinoid type-1 receptors (CB1Rs), making it a plausible substrate for chronic THC-induced alterations in sleep-regulating thalamic circuits. We developed a chronic vaporized THC exposure model and hypothesized that repeated THC exposure would produce behavioral tolerance and withdrawal-associated behavioral adaptations comparable to established intraperitoneal (IP) THC paradigms. Adult male and female C57BL/6J mice (3-4 months old) were exposed to THC vapor (100 mg/mL in propylene glycol) or vehicle for 7-10 days. This paradigm produced acute plasma THC concentrations of approximately 50-100 ng/mL,

comparable to levels achieved in established THC administration models. Locomotor activity was assessed across repeated exposures to quantify behavioral tolerance. Novel object recognition (NOR) was assessed longitudinally in the same animals at 55 h and 72 h withdrawal. Previously published EEG/EMG recordings from mice receiving chronic THC (10 mg/kg, IP) were used to assess withdrawal-associated alterations in sleep architecture. Chronic THC vapor exposure produced robust locomotor tolerance (n = 12/group), with significant effects of treatment and time (two-way ANOVA, both $p < 0.0001$). In a comparable chronic THC exposure paradigm using IP administration, withdrawal significantly altered NREM sleep architecture (n = 6-9/group, $p < 0.05$). NOR performance at 55 h withdrawal did not differ between groups ($p > 0.05$). At 72 h, THC-exposed mice exhibited a higher discrimination index than vehicle controls ($p = 0.0337$); however, control performance also differed between sessions, suggesting a potential circadian or interval effect. Accordingly, this finding is considered exploratory. These findings demonstrate that chronic THC vapor exposure produces robust behavioral tolerance comparable to established IP THC models and support the utility of vapor administration for studying cannabis-related neuroadaptations. Together with evidence for withdrawal-associated sleep disruption, these data provide a foundation for investigating TRN CB1R signaling as a potential circuit mechanism linking chronic THC exposure to alterations in sleep and cognition.

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Topic: G.07. Biological Rhythms and Sleep

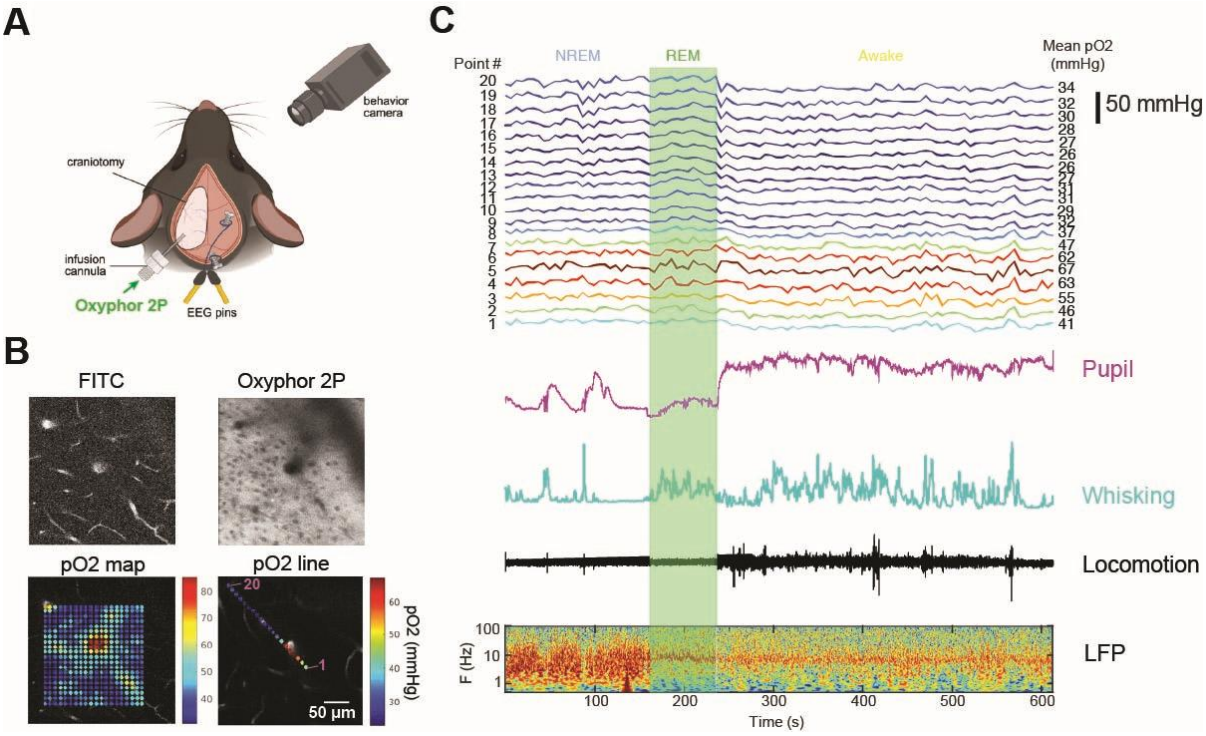
Support: 5R01NS108472-02
1U19NS123717-01

Title: Spatially resolved brain oxygen dynamics across brain states in healthy and Alzheimer's disease mice

Authors: *N. FOMIN-THUNEMANN[1], R. TANG[1], V. PUAR[1], A. GARCIA[2], B. RAUSCHER[1], J. JIANG[1], P. MACHLER[3], M. THUNEMANN[1], D. A. BOAS[1], A. DEVOR[1]; [1]Biomed. Engin., [2]Pharmacology, Physiol. & Biophysics, Boston Univ., BOSTON, MA; [3]Neurosciences, UCSD, La Jolla, CA

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, vascular dysfunction, and disrupted sleep. Cerebrovascular abnormalities, including reduced cerebral blood flow (CBF), impaired neurovascular coupling, blood-brain barrier dysfunction, and capillary stall perfusion deficits (CSPDs), may compromise oxygen delivery to the brain and contribute to neuronal injury. Brain state transition is coupled

with CBF changes reflecting brain-state-specific metabolic demands. What still remains unknown is the degree of variation in tissue oxygenation across levels of alertness and during sleep, and how these dynamics are altered in AD. To address these questions, we used two-photon phosphorescence lifetime microscopy (2PLM) with the oxygen-sensitive probe Oxyphor 2P to measure partial pressure of oxygen (pO_2) in brain tissue at micrometer-scale resolution in 12-18month-old APP/PS1 mice and control littermates. Chronic infusion cannulas enabled repeated delivery of Oxyphor 2P into the somatosensory cortex. Simultaneously, brain state was monitored using EEG recordings together with measurements of pupil diameter, whisking, and locomotion, allowing assessment of tissue pO2 dynamics across wakefulness, NREM sleep, and REM sleep. In AD mice, we used OCT to identify intermittently stalling capillaries for later examination with 2PLM. In healthy mice, tissue pO_2 was surprisingly stable despite behavioral and sleep-state transitions. At the same time, we observed local pO_2 transients that occurred independently of brain state. Tissue oxygenation modestly increased during sleep, peaking during REM. In AD mice, tissue surrounding stalled capillaries exhibited repeated, significant reductions in pO_2, providing direct evidence that CSPDs generate local oxygen deficits. These data indicate that oxygen supply closely tracks demand during spontaneous activity and transitions between brain states. Our AD data provide direct evidence that CSPDs generate local oxygen deficits in cerebral tissue.



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Nanosymposium

NANO43: Prefrontal Cortex in Learning and Decision-Making

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Topic: I.03. Decision Making

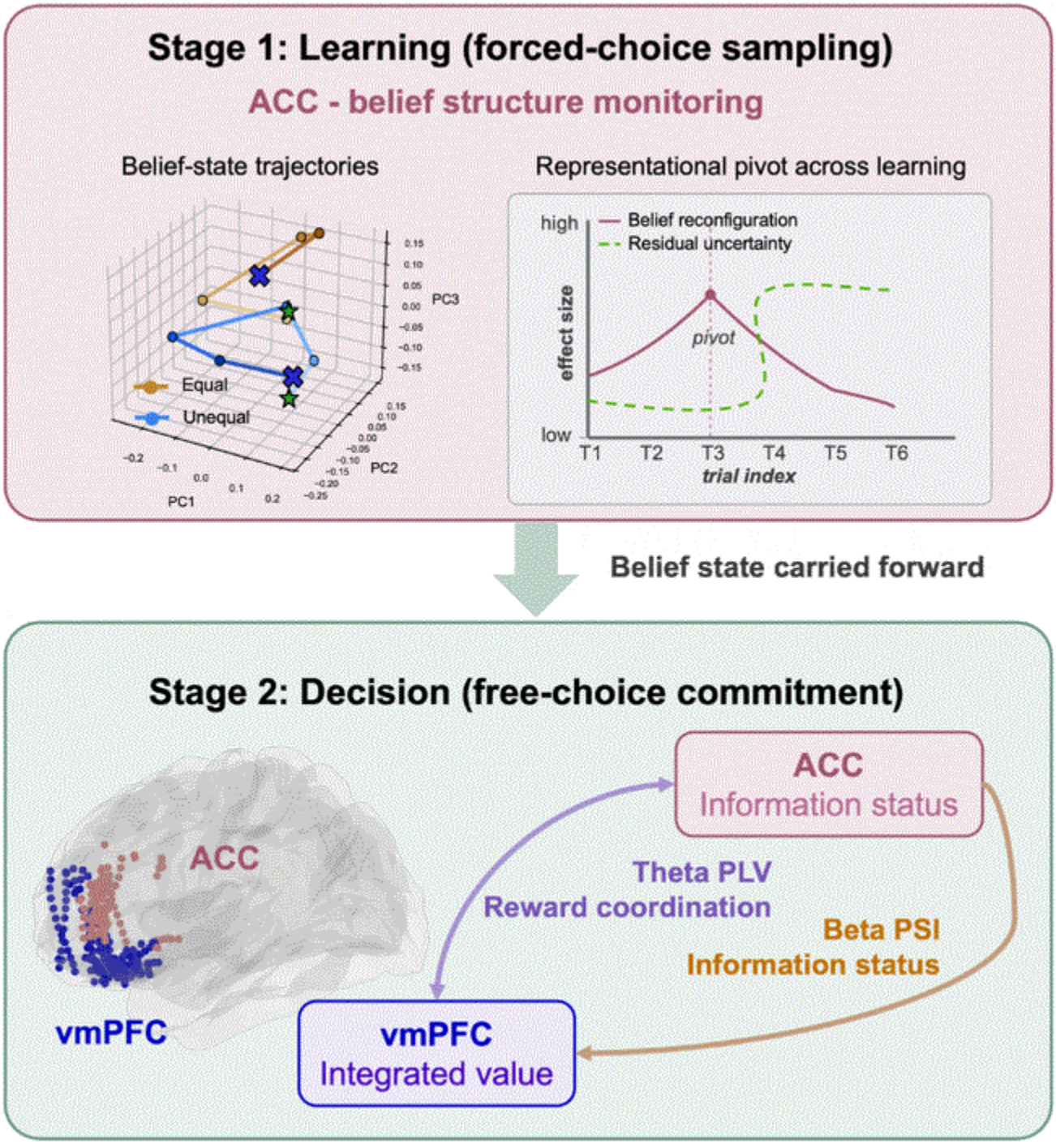
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Title: Prefrontal coordination of belief monitoring and value integration in human exploration

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Abstract: Prefrontal Coordination of Belief Monitoring and Value Integration in Human Exploration
Keyu Hu[1], Haoming Zhang[1], Changlin Bai[1], Yangchun Chen[2,3], Xiaobin Zhang[2,3], Jiayu Cheng[1], Fengpeng Wang[2,3], Mo Chen[1], Yi Yao[2,3], Haiyan Wu[1*]
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Adaptive exploration requires people to evaluate not only expected reward, but also the information that actions can reveal. How the human prefrontal cortex maintains evolving belief states during learning and converts them into subjective value at choice remains unclear. We recorded stereoelectroencephalography (SEEG) from 25 patients with epilepsy performing a explore-exploit task that dissociated reward expectation from sampling-history-dependent information. A computational reinforcement-learning model showed that choices were better explained by an integrated value signal combining reward and information status than by reward alone. Neural analyses focused on the ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC). During free choice, vmPFC broad-band gamma activity encoded subjective value, while also carrying separable reward and information components. In contrast, ACC beta activity preferentially tracked information status before choice. Inter-regional coupling analyses revealed frequency-specific prefrontal coordination: information status modulated ACC-leading beta-band coupling with vmPFC, whereas reward value was associated with theta-band phase locking between ACC and vmPFC. During the preceding forced-sampling phase, low-dimensional population trajectories in ACC, but not vmPFC, were shaped by the task's information structure. ACC activity also reflected belief dynamics across learning, separating belief-reconfiguration trials at the midpoint of sampling and later aligning with residual uncertainty as beliefs stabilized.
Together, these intracranial findings identify a two-stage prefrontal architecture for human

exploration: ACC monitors evolving belief states and information status, then coordinates with vmPFC, where reward and information are integrated into a subjective value signal that guides explore-exploit decisions.



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Nanosymposium

NANO43: Prefrontal Cortex in Learning and Decision-Making

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Topic: I.03. Decision Making

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Title: Scale Invariance in Economic Choices: Behavioral Evidence, Neuronal Origins, and Decision Models

Authors: *M. BARRETTO-GARCÍA, C. PADOA-SCHIOPPA;
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Abstract: It is often assumed that economic choices are driven by the value difference. Here we examined 16 data sets from 9 rhesus monkeys performing 7 different tasks. Consistently, choices were better explained as driven by the log value ratio - a trait termed scale invariance. In principle, scale invariance might be imposed by sublinear value functions (Weber-Fechner law). However, value-encoding neurons in orbitofrontal cortex (OFC), whose activity is causal to choices, represent values linearly (Rustichini et al., 2017). Hence, we propose that scale invariance emerges during value comparison. We then examined three leading models describing this process - a biophysically realistic model of spiking cells (Wang, 2002), the mutual inhibition model (Wong and Wang, 2006; Hunt et al., 2012), and the drift-diffusion model (Ratcliff and McKoon, 2008; Krajbich et al., 2010). In their standard version, which assumes that input noise is independent of input strength, all three models fail to account for scale invariance. However, if input noise is assumed proportional to the input strength (Poisson variability), as observed in OFC neurons encoding the offer values (Tolhurst et al., 1983; Conen and Padoa-Schioppa, 2015), all three models closely reproduce scale invariance. The theory presented here provides a new interpretation for the Weber-Fechner phenomenon in the context of economic decisions.

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Nanosymposium

NANO43: Prefrontal Cortex in Learning and Decision-Making

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Presentation Number: NANO43.03

Topic: I.03. Decision Making

Support: NSF CAREER Award BCS-2238711

Title: Advantages of Reflecting on Success and Failure During Learning

Authors: *Y. HUANG, C. J. HONEY;
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Abstract: Why do people tend to ruminate more on failures than successes? This phenomenon has been observed in people pursuing personal goals, solving puzzle tasks, and public speaking (Roberts et al., 2013; Kaap-Deeder et al., 2016; Blackie & Kocovski, 2018). In both reinforcement learning models and mammalian brains, experience replay is generally thought to accelerate learning. Thus, one possibility is that rumination corresponds to experience replay, and replaying failures leads to more learning, than replaying success experiences. However, neuron-level experience replay does not appear to be increased for failure trials over successes (Zheng et al, 2021). Perhaps simple experience replay is not sufficient to explain the phenomenon. We propose that “reflection”, a process that extracts causal relationships and restructures goals, boosts learning and task performance, especially following failures. Therefore, we developed a modeling framework to test whether reflecting on failures versus successes differentially enhances learning compared to simply replaying past experiences. Using a grid-world navigation task, we compared a reinforcement learning agent's performance under reflection versus replay conditions. The agent first explored a set of environments, then either replayed past trajectories or reflected on them. Through reflection, the agent could infer cause-effect relationships (e.g., "green button opens the exit door") and identify novel subgoals, thereby restructuring its reward function. Preliminary results indicated that the agent learned the optimal route faster when reflecting on failure experiences compared to only replaying those experiences. In contrast, reflecting on successes offered minimal advantage beyond what was gained from replaying already-effective behaviors. In ongoing work, we are continuing to characterize where, how, and why explicit reflection offers distinct advantages over implicit replay mechanisms.

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Nanosymposium

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NYU Shanghai Boost Fund

Title: Neural Circuit Mechanisms of Representation Transformation in Sequential Economic Choice

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Abstract: Choices under sequential offers require the brain to encode a current offer, maintain its value, and compare it with a later offer before selecting an action. Prominent models explain choice through attractor dynamics that maintain stable, identity-preserving representations of offers and choices. However, recent recordings from monkey orbitofrontal cortex during sequential-offer economic choices revealed a different signature: strong order-based choice signals and weak identity-based signals. To identify the circuit principles underlying this computation, we trained recurrent neural networks to perform an order-based choice task and reproduce the observed psychometric behavior. The trained networks developed overlapping value representations across offer identities and dynamically reformatted the first offer across delay periods into a memory signal that could be compared with the incoming second offer. Low-dimensional latent-circuit inference revealed complementary roles for feedforward and recurrent connectivity: feedforward weights mapped different offer types onto a common value scale, whereas asymmetric recurrent interactions between sensory and decision variables generated order-based choice signals. The model further predicted specific relationships among value coding across task phases and order-choice preference, which were confirmed in monkey data. Together, these findings identify a dynamic circuit motif for sequential-offer economic choice that differs from classical attractor accounts and reveal a general principle by which recurrent circuits can flexibly reformat value representations across computational stages to support memory-guided decisions.

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Nanosymposium

NANO43: Prefrontal Cortex in Learning and Decision-Making

Location: WCC Rm 143

Time: Wednesday, November 18, 2026, 8:00 AM - 10:45 AM

Presentation Number: NANO43.05

Topic: I.03. Decision Making

Support: NIH Grant P50MH106435

Title: Drift Diffusion Modeling of Probabilistic Approach-Avoidance Decision-Making in Severe OCD

Authors: *P. STETSON[1], M. A. SHERIF[3,4], Z. CHENG[5], S. MILBACK[6,7], D. S. HASSAN[6,7], N. C. MCLAUGHLIN[2,6], A. SHENHAV[5], S. RASMUSSEN[2,6];
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Abstract: Obsessive-compulsive disorder (OCD) is associated with maladaptive approach-avoidance behavior and altered decision-making under uncertainty. We used the Probabilistic Approach-Avoidance Task (PAAT) to examine how choices are made under competing reward and aversive outcome probabilities in individuals with severe, treatment-refractory OCD who were assessed at baseline and/or post-ventral laser capsulotomy. In the PAAT, participants chose between options with varying probabilistic reward and aversive consequences, generating decisions under uncertainty spanning low to high approach-avoidance conflict. Participants were 12 adults (3 female, 9 male; mean age at baseline = 39.0 ± 10.1 years). Drift diffusion modeling (DDM) was employed to estimate latent decision parameters: drift rate (v; evidence accumulation speed), boundary separation (a; decision threshold/caution), starting bias (z), and non-decision time (t), with hierarchical effects applied to v, a, and z to capture group- and participant-level effects. Models evaluated session (pre-/post-surgery), conflict congruency (high-conflict: reward paired with high aversive risk), OCD symptom severity, measured with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and reward and aversive probability components. All fitted models demonstrated good convergence (R-hat ≤ 1.01). In a primary symptom+conflict model, high-conflict trials were associated with greater boundary separation (a) (beta = 0.144, 94% highest density interval (HDI) [0.084, 0.202]), while conflict effects on drift rate (v) were weak (beta = -0.060, 94% HDI [-0.154, 0.031]). In the same model, Y-BOCS severity showed a small positive association with a (beta = 0.047, 94% HDI [0.001, 0.094]), while effects on v were again weak (beta = 0.005, 94% HDI [-0.042, 0.052]). Session effects were limited in the current sample. These preliminary findings from an exploratory study support a link between conflict and elevated decision threshold. Notably, symptom severity was also positively associated with decision threshold, suggesting elevated decision threshold may be meaningfully related to OCD severity. If replicated, decision threshold may represent a clinically relevant computational marker of approach-avoidance decision-making in OCD.

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Nanosymposium

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Topic: I.03. Decision Making

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Title: Attention and introspection: computational modeling reveals relationship between metacognitive ability and attentional control

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Abstract: Attentional Blink (AB) is a well-documented phenomenon where individuals following a visual target fail to detect a second target if it appears ~200ms from the first. This processing "bottleneck" appears to be nonetheless malleable. AB can be reduced through visual attention training via video games, but also interestingly, through mental training via mindfulness meditation. We wanted to test whether introspecting about one's choices, a process known as metacognition, would similarly ameliorate the AB. We hypothesized that individual differences in metacognitive ability could limit the effect of metacognition on AB. We addressed this by measuring AB before and after completing a task where subjects engaged in metacognition. 450 participants, split across three groups (confidence task/control task/no task), completed the experiment online. AB was measured via rapid serial visual presentation task, where participants viewed a fast stream of visual stimuli and had to identify an initial target (T1) before detecting a second target (T2). They completed the AB before and after an orientation categorization task. In this task, participants were presented with a single foveal Gabor, oriented to the left or right (0.5°-5°) and varying between two contrast levels. All participants indicated the Gabor's orientation (left or right). The confidence task group then reported their confidence that their categorization was correct on a 1-4 scale, the control task group reported on its contrast, and the no task group made no secondary report. AB data was fit to a signal detection theory (SDT) linear model through hierarchical Bayesian estimation, to derive individual-level decision criterion and decision sensitivity parameters and their change after the task. Confidence data was fit to a computational process model of confidence (CASANDRE) to derive individual parameters of metacognitive ability. We found no differences between group-level changes in decision sensitivity or decision criterion. All groups showed an increase in decision sensitivity, indicating an improvement in performance likely due to repetition rather than the metacognitive intervention. At the individual level, greater metacognitive ability related to higher baseline AB decision sensitivity. This result replicated findings in two prior samples. We also found an association between metacognitive ability and shift in AB decision criterion, with more conservative reporting of T2 in the second AB task. Given that greater metacognitive ability relates to enhanced attentional control, future studies could address whether metacognition and visual attentional control share common mechanisms.

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Topic: I.03. Decision Making

Title: Human-like simple choice and fixation behavior emerges from attractor dynamics in reinforcement-learning-trained RNNs

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Abstract: Growing evidence from neuroeconomics and computational neuroscience suggests that value-based decisions emerge from a dynamic process in which the brain samples noisy evidence by allocating attention across alternatives and integrates that evidence to make a choice. While evidence accumulation models such as the Drift-Diffusion Model capture reaction time distributions and the speed-accuracy tradeoff, they treat the information-gathering process as external to the decision variable.Work on human gaze patterns during choice tasks has revealed that the information-gathering process strongly influences choice behaviors with, for example, visual attention systematically biasing decisions toward the attended target. Furthermore, previous work has found that fixations to the available options are not randomly allocated but rather directed in a way that mirrors optimal information gathering. The circuit- and dynamical-level computations that jointly account for attention allocation and evidence integration therefore remain poorly understood.To address these limitations, we trained recurrent neural networks (RNNs) via reinforcement learning to perform simultaneously binary and trinary simple choice tasks to maximize cumulative reward by jointly learning a sampling strategy and a stopping rule. We then compared the networks' learned fixation allocation and choice strategies to those of humans performing the same tasks in an eye-tracking setup.The trained RNNs closely replicated the full range of human psychometric signatures across both task contexts, including reaction time distributions, choice probabilities as a function of relative item ratings, and gaze-switching dynamics. Analyzing the networks as dynamical systems revealed winner-take-all attractor dynamics: incoming evidence warps the nullclines of the system and collapses the central saddle point, driving the system toward a choice attractor. Mapping the pseudo-energy landscape along the decision axis showed that stimulus onset tilted the system toward a low-energy commitment state, while removing the stimulus left the network in a shallow local energy minimum state capable of shifting quickly given subsequent contradictory evidence.These findings show that RNNs optimized for sequential choice can help to unify evidence accumulation and active attention allocation into a single learned policy and naturally discover heuristically optimal, human-like strategies. Moreover, these policies are implemented via interpretable attractor dynamics, which mirror classic models of visual discrimination.

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Nanosymposium

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Title: A model-free account of selective attention: Unifying value and precision signaling via dopamine-driven uncertainty

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Abstract: Computational reinforcement learning (RL) frameworks traditionally utilize dopamine-encoded reward prediction errors (RPE) to update value estimates, but they struggle to account for selective attention and dynamic feature weighting without relying on complex Bayesian priors or explicit model-based architectures. While optimal learning theories suggest that selective attention should be scaled with feature precision (inverse variance), a major biophysical question remains: how do biological agents estimate feature-level variance within unknown or volatile environments?

To address this gap, we present Precision-Weighted RL (PW-RL), an algorithmic framework demonstrating that standard temporal-difference (TD) RPE signals can simultaneously compute both feature values and uncertainty. In this unified architecture, the calculated uncertainty prediction error is derived from the RPE to dynamically update a running estimate of feature variance. The relative precision of each feature then modulates attentional allocation by scaling feature learning rate and its weight contribution to the total expected value of an option.

To validate the computational efficacy of PW-RL prior to human empirical testing, we conducted behavioral simulations comparing PW-RL against standard TD reinforcement learning (TDRL) across three canonical task variants: Blocking, Latent Inhibition, and Environmental Volatility. Standard feature-based TDRL fundamentally failed to replicate known human behaviors and adapted poorly to environmental shifts. Conversely, PW-RL natively reproduced these behaviors. In the Blocking variant, high precision from an established feature successfully suppressed learning of novel non-informative features. In the Latent Inhibition variant, unreinforced pre-exposure appropriately drove down estimated precision, resulting in a characteristically delayed learning curve when the feature became informative. Finally, in the Volatile variant, PW-RL dynamically accelerated learning in response to elevated variance, rapidly tracking volatile rewards while preserving the value expectation of stable features.

These preliminary simulations demonstrate that an RPE-driven computation can track feature variance natively, establishing a single, unified dopaminergic mechanism capable of bridging value-based learning and selective attention without requiring pre-specified priors or explicit environmental models. Ongoing work leverages these distinct mathematical prediction curves to fit human choice behavior, concurrent eye-tracking metrics, and sub-second intraoperative dopamine fluctuations in humans.

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Title: How learned expectations shape brain-wide responses

Authors: *A. LIU[1], M. SCHARTNER[2], I. BRAIN LAB[3], I. R. FIETE[1];
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Abstract: Expectations stemming from prior knowledge have long been known to influence stimulus processing and decision-making. Empowered by brain-wide recordings during a two-choice sensory decision-making task from the International Brain Laboratory, we sought to identify the form of expectation-based modulations and how they influence ongoing computations. To discern where, when, and how prior knowledge about the stimulus - known to be stored in the brain over the inter-trial period - influences brain activity over the arc from stimulus processing to choice selection and action generation, we disentangled the encoding of the highly correlated stimulus, choice, and prior variables as sensory processors, choice/integration processors, and movement generators. We examined which brain regions were modulated by prior expectations and at which point in the task, and characterized whether those modulations take the form of biasing initial activations or response gains. We found that the activities of choice/integrators and movement generators were influenced by prior expectation, while purely stimulus processors were not significantly modulated by prior expectation. In addition, we found that expectation-based modulation takes the form of both initial activity bias and gain modulation in integration/choice computations and in movement generators. We further find that the brain-wide recordings reveal an emergent simplicity: A few-parameter mechanistic neural circuit model captures the population dynamics of stimulus response, integration/choice

processing, and action initiation, as well as their modulations by the prior. After fitting to physiology, the model's behavior predicts the psychometric and chronometric behavior of mice with no additional parameters. It reveals that the larger bias and gain modulations of movement initiators relative to integration/choice in the data and model is inherited by amplifying integrator/choice inputs rather than being an additional expectation-based effect. Collectively, our results characterize in fine spatiotemporal detail and brain-wide breadth the mechanisms and loci where prior expectations influence cognition, while the novel synthesis between large-scale electrophysiology and mechanistic modeling reveals an organizing simplicity behind perceptual decision making across the brain.

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Topic: I.03. Decision Making

Support: Medical Research Council MR/V033492/1

Title: Computational dissociation of subgenual anterior cingulate cortex and dorsolateral prefrontal cortex contributions to affective decision making

Authors: *A. GARCIA VERGARA[1], R. N. CARDINAL[2], C. M. WOOD[3], K. G. MULVIHILL[3], A. C. ROBERTS[3];
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Abstract: Dorsolateral prefrontal cortex (dlPFC) and subgenual anterior cingulate cortex (sgACC) are both implicated in depression, showing opposing patterns of abnormal activity that can normalise upon successful treatment. In common marmosets, inactivation of Brodmann area (BA) 46 of dlPFC and overactivation of BA25 of sgACC produce overlapping behavioural phenotypes, including increased threat responsivity and blunted reward responsivity. However, their distinct causal contributions to affective decision-making remain unclear.To address this, we developed computational models to characterise these regions' causal contributions to affective decision making across reward and threat-related contexts. Data from 25 marmosets tested on ambiguous cue tasks (ACT), a probabilistic reward task (PRT), and a progressive ratio task (PR) were interpreted using computational models of evidence accumulation, reinforcement learning, and motivational vigour.In reward contexts, both manipulations produced similar effects, including reduced willingness to work for reward, enhanced bias towards high reward under ambiguity, and increased reward bias when differences between available rewards were large. However, computational modelling suggested distinct underlying mechanisms: BA25 overactivation reduced reward learning and reward-induced arousal, whereas BA46 inactivation

enhanced reward-value weighting during choice and increased effort sensitivity. Importantly, the manipulations diverged when reward differences are small: BA25 overactivation blunted reward bias, whereas BA46 inactivation yielded mixed effects. In punishment contexts, the manipulations had opposing effects under ambiguity, with BA25 overactivation enhancing avoidance, and dlPFC-46 inactivation enhancing reward responses. Computational modelling revealed preferential evidence accumulation towards avoidance following BA25, and towards reward following BA46 inactivation.Together, these findings demonstrate dissociable but complementary roles for sgACC and dlPFC in affective decision making. Overactivation of BA25 seems to induce negative changes to affective valuation characterised by enhanced threat sensitivity and blunted baseline reward sensitivity. The increased responsivity to high reward observed in some contexts may therefore reflect a contrast effect, whereby larger rewards become disproportionately valued in an overall blunted reward context. In contrast, BA46 disruption appears to preclude the flexible integration of competing value signals during decision-making, biasing behaviour towards simpler reward-approaching policies.

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Nanosymposium

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Title: Neural correlates for change of mind

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Abstract: Intentions can often be revised or changed even without new external information. This internal process, called a change-of-mind (CoM), is a key aspect of cognitive flexibility. Despite its importance, the neural mechanisms underlying CoM at the whole-brain level in humans remain poorly understood. Additionally, how local brain dynamics influence CoM behaviors remains unclear. In this study, we hypothesize that the frontoparietal network, which operates on a large scale, plays a critical role in supporting CoM, and that differences in local brain dynamics may explain individual variations in CoM behavior.To test our hypotheses, we

conducted an fMRI experiment using a perceptual decision-making task. Twenty-eight right-handed healthy participants were asked to judge the direction of random dot motion (left or right) and indicate their decision by moving a cursor to the appropriate target with moving their finger across a touchpad. Participants could revise their initial decision before reaching the target, allowing us to analyze CoM behaviors.We observed CoM trials at a frequency of 19.9 ± 10.1% (mean ± SD) across participants. The fMRI analysis indicated increased activity during CoM trials compared to non-CoM trials in frontal and parietal areas, including the right precuneus, superior frontal gyrus, supramarginal gyrus (SMG), angular gyrus, and left middle frontal cortex (cluster-level FWE-corrected $P < 0.05$). In contrast, during non-CoM trials, we observed increased activity in the left posterior insula, bilateral anterior cerebellum, and left medial frontal cortex (cluster-level FWE-corrected $P < 0.05$). Moreover, resting-state fMRI data were collected to assess whether local brain dynamics, measured by the intrinsic neural timescale (INT), could explain individual differences in CoM tendencies. Notably, the INT of the right SMG was significantly linked to both brain activity during CoM trials and the CoM rate across participants (brain activity: $r = 0.50$, $P = 0.004$; CoM rate: $r = -0.56$, $P = 0.002$). Mediation analysis revealed that a longer INT of the right SMG increased its activity during CoM trials, which subsequently led to a lower CoM rate ($P = 0.015$ for the mediation effect).These findings enhance our understanding of the large-scale brain networks and local dynamics that underpin decision-making flexibility.

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Title: Multimodal alignments of in vivo imaging and spatial biology datasets at cellular resolution

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Abstract: Parallel revolutions in intravital microscopy and spatial biology techniques have respectively enabled large-scale recordings of cellular dynamics in live animals and multi-dimensional molecular profiling at single-cell resolution. However, due to the challenges of aligning data from different modalities at cellular resolution, these two transformational approaches have generally been applied on separate biological samples, stymying the ability to link activity patterns and molecular attributes in the same exact cells. To enable routine, multimodal investigations of cells' in vivo dynamics and molecular content, we created TRU-FACT (Total Registration Under Functional Activity, Connectivity, and Transcriptomics), a broadly applicable experimental and computational pipeline for registering large populations of individual cells across intravital imaging and spatial biology datasets. The pipeline combines three key innovations: an optomechanical tissue handling and alignment method to parallelize specimen planes, a graph-theoretic method to register individual cells based on their geometric relationships to neighboring cells, and a statistical framework that provides for each cell an a posteriori probability of correct registration. We validated TRU-FACT with several preparations for imaging neural Ca2+ activity in cortical and deep brain areas in head-fixed and freely behaving mice, RNA-barcode-expressing viruses for labeling neural projections, and low- and high-plex spatial transcriptomic methods, yielding >10,000 total cell matches. Overall, TRU-FACT constitutes a routine, scalable, multimodal discovery platform that is applicable to diverse tissue-types and spatial biology techniques, thereby enabling multiscale analyses of many complex biological systems.

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Topic: J.04. Physiological Methods

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Title: A polymer fiber bundle reveals enteric neuron dynamics during colitis

Authors: *G. EBERLY[1], T. CANNON[2,5], N. BIGLARI[2], K. NAGAO[2], E. VARGAS PANIAGUA[6], Z. SULLIVAN[3], P. ANIKEEVA[4];
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Abstract: The enteric nervous system (ENS) locally regulates gastrointestinal (GI) motility and communicates with the central nervous system (CNS) to influence complex behaviors, like feeding and arousal. Dysregulation of the ENS not only drives digestive and metabolic disorders, but also contributes to GI symptoms associated with neurodevelopment, neurodegenerative, and neuroimmune conditions. However, full physiological and pathophysiological understanding of ENS circuits is precluded by a lack of technologies that can record from the ENS over several weeks. Here, we present an endoscopic system that enables repeated, non-surgical imaging of the ENS in the murine colon. Integrated with a microfluidic and capable of dual-color imaging, our system, for the first time, enables causal manipulation and imaging of the mammalian GI tract in live animals. We use our colonscope system to track daily changes in ENS activity, vasculature archetecture, and local motility during colitis onset and during recovery in the Calb2-Cre::GCaMP8s mouse line. We show that during colitis, Calb2 neuron activity shifts towards a lower baseline frequency, that colonic vasculature actecuture is disupted, and colonic motiltiy slows. As the animal recovers from colitis, these features gradually return to baseline. Overall, our colonoscope system is a powerful tool that will power further study of the enteric circuits that control GI function.

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Title: Stable 2-Photon imaging of the tissue-device interface across cortical layers reveals dynamic vascular remodeling and heterogenous microglial response.

Authors: *A. K. GORMALEY[1,2], A. VAZQUEZ[3,2], T. CUI[2];
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Abstract: Intracortical microelectrode arrays (MEAs) have the potential to deliver precise and personalized therapies for patients such as restoring motor and sensory function and localizing epileptogenic zones. While these devices enable recording and stimulation with high spatial

resolution, their chronic performance remains highly variable. Ex vivo histology studies have found gliotic encapsulation around devices. This creates a conductive barrier between the electrodes and the neuronal targets. However, previous analysis has shown an inconsistent relationship between the size of the gliotic encapsulation and the signal-to-noise ratio [Kozai 2014]. While in vivo 2-Photon imaging (2P) has shown the microglia response to MEAs, current methods are limited to cortical layer 2/3 and hindered by reduced imaging quality over time [Kozai 2015]. Thus, new methodology is required to provide crucial insight into the mechanisms leading to loss of signal. To overcome these challenges, we have developed a strategy using 2P imaging through microprisms to enable chronic, high-resolution imaging of the tissue-device interface across all layers of the mouse cortex. To implant the microprism window, the edge of the microprism is inserted into a single incision. The tissue underneath the reflective hypotenuse is compressed while the tissue in the imaging field remains intact. After approximately 5wks of healing, the imaging quality stabilizes for upwards of 6 months and the microglia beyond 50μm are homeostatic [Yang 2021]. To enable MEA implantation after healing, a resealable port is laser-etched into the cranial window prior to the initial surgery. In this study we implanted the microprism+port in N=3 tg mice (CX3CR1-GFP Microglia, Thy1-jRGECO1a Neuronal Calcium). Mice were implanted with thin-film, flexible MEAs and N=2 animals demonstrated over 5mos. of high-resolution imaging of cells directly on the device surface. Imaging shows distinct changes in vasculature surrounding the devices and diverse microglial morphology along the surface. Our work validates the capability of this method to evaluate biomaterial strategies for promoting seamless integration and chronic performance of neural implants in the brain.

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MOST 110-2320-B-A49A-525

Title: Genetic optical sectioning enables high-density kilohertz cellular voltage imaging across millimeter-scale cortex

Authors: *T.-W. CHEN, B.-J. LIN;
Inst. of Neurosci., Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Optical sectioning is essential for imaging structure and activity in three-dimensional tissues, but existing approaches often require specialized instrumentation and impose trade-offs between imaging speed and field of view. Here we show that optical sectioning can be encoded

through gene expression. Selective Plane Expression (SPress) restricts fluorescent indicator expression to a user-defined, 20-μm-thick plane, creating a “biological light sheet” within the brain. After one-time expression patterning with a conventional two-photon microscope, SPress enables standard widefield microscopes to capture high-contrast kilohertz voltage dynamics from hundreds of densely labeled neurons across millimeter-scale cortical sheets in vivo. Configured vertically with microprisms, SPress captures cross-layer voltage dynamics spanning cortical layers 2/3 and 5, revealing behavior-dependent subthreshold waves that flexibly organize neuronal firing across cortical space and layers. By shifting optical sectioning from the microscope to the sample, SPress establishes an accessible strategy for linking cellular electrophysiology to mesoscopic brain dynamics.

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Topic: J.04. Physiological Methods

Title: Enhanced High-Speed In Vivo Voltage Imaging Through Engineered Two-Photon Excitation

Authors: Y.-S. LIAO[1], G. FERRER IMBERT[3], ***E. ZARNOWSKA**[4], C. X. WANG[6], I. MACGILLIVRAY[5], M. Z. LIN[7], N. JI[2];
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Abstract: Genetically encoded voltage indicators (GEVIs) and high-speed two-photon (2P) fluorescence microscopy (FM) have significantly advanced the ability to measure neuronal membrane potential dynamics with high temporal resolution in identified neuronal populations. These innovations provide unprecedented access to neuronal activity and are critical for understanding how neuronal circuits represent, store, and transmit information in the brain. Recent ASAP-family GEVIs have demonstrated the utility of voltage imaging for large-scale action potential detection with temporal precision beyond that achievable with calcium indicators. Imaging techniques such as FACED 2P FM enable recordings from hundreds of cells at the kilohertz frame rates required to resolve fast voltage dynamics in vivo. However, voltage imaging remains fundamentally photon-limited and highly dependent on excitation conditions. While existing high-power, low-repetition-rate laser systems provide sufficient pulse energy, they are often not optimized for modern voltage imaging applications. Limitations include suboptimal wavelength alignment with voltage indicators, insufficient pulse-to-pulse stability, incomplete pulse compression at the sample, and limited integration into complex imaging systems. Together, these constraints reduce signal-to-noise ratio and limit imaging performance.

We developed and implemented a 2P excitation platform optimized for high-speed, large-field-of-view voltage imaging of ASAP-family GEVIs using FACED 2P FM. The platform consists of a Coherent Osprey laser and a multi-pass cell (MPC) module. The Osprey is a Yb-fiber laser delivering >5.5 μJ pulse energy at 1 MHz, 1030 nm, and 270 fs pulse duration. The MPC enables spectral broadening and pulse compression to improve 2P excitation efficiency. Optimized excitation conditions increased fluorescence signal intensity by approximately 3-8-fold for ASAP-family voltage indicators, enabling high-speed in vivo voltage imaging with dramatically improved signal-to-noise ratio. Enhanced pulse compression and spectral alignment increased excitation efficiency while maintaining stable imaging performance during kilohertz-rate acquisition. These results demonstrate that excitation engineering is a critical determinant of voltage imaging performance. By improving photon efficiency and signal quality, optimized multiphoton excitation expands the practical capabilities of high-speed in vivo voltage imaging and enables more reliable measurements of neuronal activity across large populations of identified neurons.

Disclosures: Y. Liao: None. **G. Ferrer Imbert:** None. **E. Zarnowska:** None. **C.X. Wang:** None. **I. MacGillivray:** None. **M.Z. Lin:** None. **N. Ji:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO44.06

Topic: J.04. Physiological Methods

Title: Calcium imaging of complex behavioral control in free-swimming zebrafish

Authors: *R. H. DOCTOR[1], H. A. BURGESS[2];
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Abstract: We are studying the neural dynamics that cause adaptive motor responses to variable sensory cues. While studying command neurons has yielded valuable insights into sensorimotor transforms, more complex circuits are often collaboratively controlled in ways that allow for graded output along several axes. Zebrafish have two startle responses. The short-latency c-start (SLC) is controlled by a command neuron producing maximal behavior, while the long-latency c-start (LLC) is controlled by a cluster of neurons producing adaptive and energy-efficient behavior at the cost of increased processing time. As this behavior is graded and multidimensional, yet easy to measure, the LLC circuit is a valuable model to study population encoding at the cellular level in a sensorimotor interface. However, zebrafish rarely produce LLCs when immobilized for confocal calcium imaging. To examine this circuit, we have built a 'Swimscope': a low-cost microscope that noninvasively images neuronal activity in free-swimming zebrafish larvae. We first designate a range of starting positions from which a larva is likely to end under the imaging area after performing an escape. Once the larva is correctly positioned, we stimulate an escape using an acoustic stimulus while imaging behavior using a

high-speed camera. After completing an escape, larvae pause for several hundred milliseconds. During this period, we use a high-speed z-scan to image GCaMP fluorescence in a whole brain volume in under one second with single-cell resolution using widefield imaging. We image unstimulated brains as references. To compensate for non-signal change in perceived fluorescence between images, we include a pattern of GFP-expressing neurons to normalize to, in addition to deconvolving the images. We combine behavioral and neuronal imaging to determine the schema by which the control cluster codes differing motor output. This system avoids anesthesia, immobilization, and vestibular distortion and minimizes bright light exposure. Using the Swimscope, we have shown that the LLC circuit, previously described as suppressed by SLC activation, can activate to allow larvae to perform a 'double c-start'. We are now using the Swimscope to examine how LLC circuit activity maps to the kinematics of LLC behavior.

Disclosures: R.H. Doctor: None. **H.A. Burgess:** None.

Nanosymposium

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Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

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Topic: J.04. Physiological Methods

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The Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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Title: Utilizing Human Astrocyte-Neuronal Spheroids ("Asteroids"), A Fast, Scalable Platform for Electrophysiological Modeling of Neurodevelopmental Disorders

Authors: *H. WEISBLUM NEUMAN[1,2], M. C. CONDRO[1], C. M. MCCRIMMON[3], R. A. SAMARASINGHE[1,3], H. I. KORNBLUM[1];
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Abstract: Rapid and reliable human in vitro models are critically needed to study neurodevelopmental disorders. While cerebral organoids have become valuable tools, their long maturation time limits scalability and experimental throughput. To overcome these limitations, we are investigating the recently described "asteroid" model that utilizes transcription factor-induced astrocytes and neurons derived from human pluripotent stem cells to explore the role of mTOR signaling in neuronal connectivity.
Asteroids were generated from hESC using an established differentiation protocol adapted from Patel et al. (2025), using inducible NFIA and SOX9 for astrocytes or NGN2 for neurons yielding three-dimensional structures composed of 30% excitatory neurons and 70% astrocytes. Following doxycycline induction (2 μg/mL) for 14 days, mixed cultures were maintained as

spheroids for 28 days before neuronal activity was assessed. Activity was evaluated using two complementary approaches: live calcium imaging following transduction with the genetically encoded calcium indicator GCaMP, and extracellular electrophysiological recordings using multi-electrode arrays (MEA). MEA data acquisition and quantitative analysis were performed using a dedicated pipeline for assessing network activity and connectivity.
Asteroids exhibited robust spontaneous electrical activity as early as three weeks post-differentiation, representing a substantially accelerated timeline compared to conventional brain organoids. This activity was sustained over long-term culture and remained stable and detectable for at least nine weeks. We quantified the number of active neurons and characterized network connectivity in each asteroid, enabling both cross-sectional comparisons between asteroids at a given time point and longitudinal analyses of individual asteroids across time. Preliminary studies with rapamycin treatment revealed no overt changes in network activity under these control conditions.
Human astrocyte-neuronal asteroids constitute a rapid, scalable, relatively electrophysiologically mature in vitro platform for modeling human brain function and disease. This system, together with our network analysis pipeline, holds strong potential for mechanistic studies and drug screening applications.

Disclosures: H. Weisblum Neuman: None. **M.C. Condro:** None. **C.M. McCrimmon:** None. **R.A. Samarasinghe:** None. **H.I. Kornblum:** None.

Nanosymposium

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Topic: J.04. Physiological Methods

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Title: NeuroMatrix Arbitrarily Configured 3D Neural Probes for Volumetric Brain Interfacing

Authors: *Y. CAI[1], J. LI[2];
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Abstract: Volumetric neural recording requires electrode arrays that can access multiple brain depths without increasing tissue disruption or manufacturing complexity. Planar MEAs enable high-throughput with ten thousand channels, while Utah arrays provide robust deep penetration. However, neither approach achieves simultaneously high spatial coverage and depth resolution required for customable neural mapping. Here we report NeuroMatrix, a self-shadow masked

two-photon polymerization strategy for fabricating three-dimensional microneedle arrays with directly programmable height, diameter, pitch and tip geometry. In this approach, printed overhangs serve as built-in shadow masks during directional metal deposition, and a secondary printing step encapsulates the conductive traces while preserving exposed recording tips. This design removes the need for conventional lithographic alignment on high-aspect-ratio three-dimensional surfaces and allows different needle heights to be encoded directly into a single digital print. We fabricated 121-channel microneedle arrays with diameters of (5-100 um), high aspect ratio 10-60, and user-defined spatial layouts. Acute and chronic rat cortical recordings and histological assessment further supported the feasibility of the printed arrays for intracortical interfacing. These results establish self-shadow 2PP printing as a simple and geometry-programmable route to depth-configurable neural probes.

Disclosures: Y. Cai: None. **J. Li:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

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Presentation Number: NANO44.09

Topic: J.04. Physiological Methods

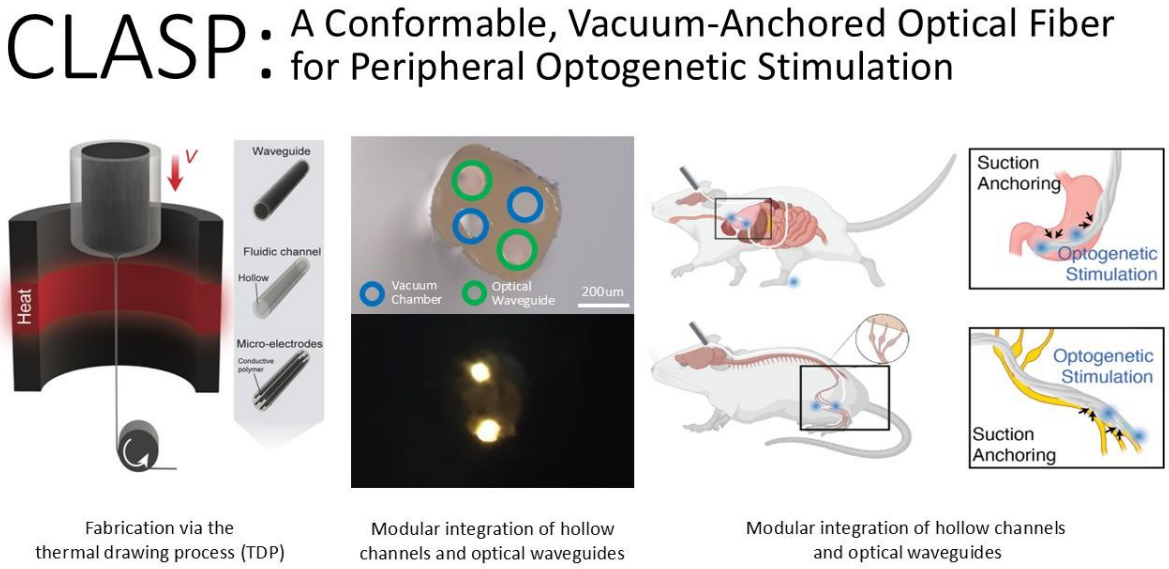
Support: National Research Foundation of Korea (RS-2026-25474579)

Title: CLASP: A Conformable, Vacuum-Anchored Optical Fiber for Peripheral Optogenetic Stimulation

Authors: *B. AHN[1], Y. KIM[3], S.-Y. KIM[1], S. PARK[2];
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Abstract: Optogenetics enables cell-type-specific, millisecond-precision neuromodulation, but its application to the study of body-brain physiology remains technically challenging. Peripheral nerves present physical obstacles including constant dynamic movement, tissue opacity, and variable individual anatomy. Existing cuff-style devices risk excessive transverse stress on nerves, while rigid fiber implants suffer from mechanical mismatch with soft tissue. A device that is simultaneously mechanically compliant, and capable of stable interfacing under dynamic physiological loads is therefore needed. We present the Conformable Linear Anchored Soft-pressure Probe (CLASP), a thermally drawn optical fiber designed for peripheral optogenetic stimulation. CLASP can be modularly configured to integrate vacuum-based microchambers and optical channels that enable spatially addressable, multichannel light delivery along linear and planar tissues. Negative pressure within microchambers enables reversible adhesion to the underlying tissue surface, maintaining stable contact between the optical channels and their target. The device exhibits bending stiffness comparable to peripheral nerve tissue, minimizing

mechanical mismatch at the neural interface. Ex vivo characterization demonstrated stable, repeatable suction-based anchoring on phantom tissue. In vivo implantation in Thy1-ChR2 mice confirmed that optical stimulation of the sciatic nerve reliably elicited hindpaw displacement, while negative-pressure actuation achieved reversible, repeatable adhesion to surrounding soft tissue without surgical fixation. CLASP's conformability and target-agnostic anchoring mechanism make it applicable to diverse anatomical target across body-brain physiology, including organ surfaces, neurovascular bundles, and peripheral nerves such as the vagus. Its design may serve as a platform for preclinical investigation of peripheral neuromodulation parameters across a wide range of target tissues and disease contexts.



Disclosures: B. Ahn: None. **Y. Kim:** None. **S. Kim:** None. **S. Park:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

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Presentation Number: NANO44.10

Topic: J.04. Physiological Methods

Support: NIH Grant 1UM1 MH136462
NIH Grant 5U19 NS123719

Title: New dopamine sensors for quantitative multiplexed imaging

Authors: *J. A. CHOUINARD[1], K. MAN[1], Y. JIN[1], E. C. SCOTT[1], H. LIU[1], K. FERNANDEZ[1], T. PANCANI[1], B. LODDER[2], S. MAJUMDER[1], J. TANIGUCHI[3], K. M. HAGIHARA[4], N. MANCINI[1], B. L. SABATINI[5], H. INAGAKI[1], K. PODGORSKI[4], R. YASUDA[6], J. R. WICKENS[7], L. TIAN[1];
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Abstract: Dopaminergic neurons regulate movement, motivation, reinforcement learning, and behavioral state through two distinct firing modes: rapid phasic bursts that encode salient events and reward prediction errors, and slower tonic activity that establishes baseline dopamine (DA) tone over timescales ranging from minutes to hours. Understanding how these complementary signaling modes shape neural computation requires tools capable of resolving both transient and sustained DA dynamics in vivo. However, existing genetically encoded DA sensors often lack the sensitivity, dynamic range, or quantitative capability needed to accurately measure the full spatiotemporal complexity of DA signaling, particularly tonic DA fluctuations.
To address these challenges, we developed a complementary palette of DA sensors for multimodal and multicolor imaging, including both fluorescence-intensity and fluorescence-lifetime-based approaches. First, we engineered a new generation of green dLight DA sensors with substantially expanded dynamic range and sensitivity. These sensors enable high-fidelity detection of DA release across diverse brain regions and behavioral paradigms.
Second, we developed FLIM-dLight, a red fluorescent DA sensor optimized for fluorescence lifetime imaging microscopy (FLIM), enabling quantitative measurements of DA concentration independent of sensor expression levels or optical artifacts. FLIM-dLight exhibits high brightness, high affinity for DA (neuronal EC50 = 17 nM), and a large fluorescence lifetime increase of approximately 850 ps at saturating DA concentrations. Using FLIM fiber photometry, FLIM-dLight reliably reports phasic DA transients associated with food reward consumption. Under two-photon FLIM imaging, we quantified cocaine-induced increases in both baseline and evoked DA concentrations using slice-derived calibration curves and identified regional differences in tonic DA levels between the lateral and medial dorsal striatum. Furthermore, longitudinal imaging through GRIN lenses revealed significantly reduced tonic DA levels in the dorsolateral striatum of 6-OHDA Parkinson's disease model mice, with DA replacement therapies restoring DA tone in a dose-dependent manner.
Together, these complementary intensity- and lifetime-based DA sensors establish a versatile toolkit for quantitative, multiscale measurements of DA signaling, enabling simultaneous investigation of phasic and tonic DA dynamics and providing new insights into the diverse functions of DA across neural circuits, behaviors, and disease states.

Disclosures: J.A. Chouinard: None. **K. Man:** None. **Y. Jin:** None. **E.C. Scott:** None. **H. Liu:** None. **K. Fernandez:** None. **T. Pancani:** None. **B. Lodder:** None. **S. Majumder:** None. **J. Taniguchi:** None. **K.M. Hagihara:** None. **N. Mancini:** None. **B.L. Sabatini:** None. **H. Inagaki:** None. **K. Podgorski:** None. **R. Yasuda:** None. **J.R. Wickens:** None. **L. Tian:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO44.11

Topic: J.04. Physiological Methods

Support: NSF Grant 1926804

Title: Label-free electro-optic transduction of neurophysiological signals using ion-gated graphene photonics for massive scaling of neural recording

Authors: *X. LI, Z. AHMED, H. GUPTA, V. JAIN, M. CHAMANZAR;
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Large-scale neural recording with high spatiotemporal resolution is essential for mapping distributed neural activity. However, conventional implantable electrical neural probes are constrained by electromagnetic interference, inter-channel crosstalk, electrode-tissue interface impedance, and bandwidth limitations. Label-free optical recording of electrophysiology signals provides an alternative method of neural recording without the limitations of conventional electrical neural probes. By transducing electrical activity into optical signals, right at the recording site, the routed optical signals will be immune to electromagnetic interference. Moreover, the optical signals from different channels can be multiplexed over a single common waveguide without the need to have individual wire interconnects per recording electrode. This enables truly parallel multiplexing of many channels and a path towards massively multiplexed neural recording using compact and safe implants. Here, we introduce the building block of this novel neurotechnology, which is an ion-gated graphene integrated photonic microresonator that detects electrical neurophysiological signals and converts them into an optical modulation. Extracellular potentials modulate the carrier density in the graphene, shifting its Fermi level and altering its optical conductivity, which in turn changes the transmission spectrum of the microresonator. By monitoring the modulation of transmitted optical intensity, the electrical neural signal can be inferred. Light is delivered to and collected from the sensor array through optical fibers, which significantly reduces the weight and size of the backend. Multiple sensors operating at distinct optical wavelengths are simultaneously routed through a single optical waveguide. We demonstrate detection of evoked neurophysiological signals as small as 25 μV at 3 dB SNR from mouse brain tissue and show multiplexed recording from 10 sensors on a single waveguide. We have designed an array of these sensors in the form of an implantable neural probe on a released silicon probe shank with a length of 10 mm and width of 200 μm, and a thickness of less than 100 μm. This platform establishes a scalable, label-free, optically multiplexed neural recording architecture and provides a path toward high-density implantable probes for in-vivo electrophysiology.

Disclosures: X. Li: None. **Z. Ahmed:** None. **H. Gupta:** None. **V. Jain:** None. **M. Chamanzar:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO44.12

Topic: J.04. Physiological Methods

Title: Transparent electrode arrays spanning the visible-to-NIR-I spectral range enhance neural activity visualization

Authors: *H. WANG;
Biomed. Engin., Stony Brook Univ., Stony Brook, NY

Abstract: Neural dynamics have been widely applied for decoding neural activity. In parallel, electrical stimulation is an important tool in neuroscience, neurology, and brain-computer interfaces (BCIs) for modulating neural activity. However, the mechanisms underlying neural responses to electrical stimulation remain unclear at the systems level. To address this challenge, we aim to develop a platform capable of simultaneous electrical stimulation/electrophysiology recording and two-photon imaging of neural dynamics.Herein, we present a metal-free electrocorticography (ECoG) electrode array consisting of a polyethylene terephthalate (PET) substrate, modified PEDOT conductive traces, and parylene encapsulation. The device exhibits approximately 80% optical transmittance across the visible-to-NIR-I spectral range, approaching the transparency of conventional glass (~90%), while maintaining an electrical conductivity of 1000 S/cm. The electrode array demonstrates an impedance of approximately 80 kΩ at the tissue interface. Furthermore, immunohistochemical analysis reveals no detectable expression of the pro-inflammatory microglial marker CD86 in brain tissue after 7 days of implantation, indicating biocompatibility of the electrode array.

Disclosures: H. Wang: None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO44.13

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

Support: NIH Grant 1UM1MH136462

Title: A New Suite of Genetically Encoded Fluorescent Sensors to Study Norepinephrine Release in Vivo

Authors: *S. LI[1], J. J. YU[2], S. GEORGE[2], A. ANDREONI[3], L. TIAN[4];
[1]Max Plank Florida Inst. for Neurosci., Jupiter, FL; [2]MAX PLANCK FLORIDA INSTITUTE

FOR NEUROSCIENCE, Jupiter, FL; [3]Tian Lab., [4]Biochem. and Mol. Med., Max Planck Florida Inst. for Neurosci., Jupiter, FL

Abstract: Norepinephrine (NE) plays a critical role as a neurotransmitter to regulate alertness, arousal, sensory processing, memory formation and stress response, among other high-order cognitive processes. Although noradrenergic neurons mainly reside in the locus coeruleus (LC), their projections extend brain-wide and understanding the specific role, dynamics and interaction of NE with other neurochemicals is an ongoing challenge and calls for analytical methods capable of delivering high spatiotemporal resolution with unprecedented specificity. Current NE sensors either show low affinity, poor selectivity or slow kinetics which limits their applications *in vivo*. Here we report our efforts to engineer and optimize genetically encoded fluorescent reporters for the detection of NE, based on a GPCR scaffold coupled with a circularly permuted EGFP. We focused on two types of adrenergic receptors, α_{1AR} and α_{2AR}, to provide users with a suite of sensors delivering varying degrees of affinity, selectivity, and pharmacological susceptibility. Here we present the engineering strategy, optimization, and characterization of two major lines of genetically encoded NE-sensors. We propose some examples of their applications *in vivo* to study adrenergic signaling in mouse using one and two-photon imaging in multiple brain regions, highlighting the distinct release patterns across different brains regions.

Disclosures: S. Li: None. **J.J. Yu:** None. **S. George:** None. **A. Andreoni:** None. **L. Tian:** None.

Nanosymposium

NANO44: Imaging and Recording Neural Activity

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 8:00 AM - 11:30 AM

Presentation Number: NANO44.14

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

Support: NIH F31DA056121

Title: Genetically Encoded Sensors for Multiparametric Interrogation of Intracellular Redox Dynamics

Authors: *J. D. LEE, Y. KWON, Y. WANG, A. MOGHADASI, A. BERNDT; Bioengineering, Univ. of Washington, Seattle, WA

Abstract: Despite its pervasive role in human disease, redox dysregulation remains challenging to mechanistically resolve and therapeutically target. This challenge is particularly relevant in the nervous system, where redox signaling contributes to cellular metabolism, excitability, synaptic function, and stress responses across highly compartmentalized cellular architectures. Conventional approaches in redox biology often rely on static or low-dimensional measurements, such as bulk reactive oxygen species (ROS) accumulation or endpoint biochemical assays, which fail to capture the spatially organized and dynamic nature of intracellular redox regulation. Cellular redox behavior emerges from coordinated metabolic, antioxidant, and signaling

networks operating across multiple subcellular compartments and timescales. This complexity motivates a shift from integrative steady-state measurements toward spatially and temporally resolved interrogation of intracellular redox dynamics in living systems.
Here, we present a next-generation suite of genetically encoded and chemigenetic optical probes for multiparametric redox interrogation. Leveraging spectrally distinct fluorescent β-barrel protein scaffolds alongside HaloTag-Janelia Fluor chemigenetic systems, we engineer sensors optimized for multicolor, subcellularly targeted, spectrally resolved, and fluorescence lifetime-resolved imaging. These tools enable simultaneous visualization of distinct intracellular redox pathways across cellular compartments while supporting multiplexed live-cell imaging workflows. Such capabilities are well suited to investigating compartment-specific redox regulation in complex cellular systems, including neurons and glia.
Central to this work is a structure-guided engineering framework aimed at improving allosteric coupling between the sensing and reporter domains while preserving the native molecular behavior and reaction kinetics of redox-sensing modules. Rather than maximizing signal output at the expense of molecular fidelity, we sought to maintain reaction-faithful reporting of intracellular oxidative dynamics. Fast recovery kinetics enable improved resolution of repeated oxidative perturbations, transient oxidation-reduction cycles, and rapid reductive buffering events that may be obscured by slower probes. Together, these technologies establish a framework for higher-dimensional, spatiotemporally resolved interrogation of intracellular redox biology in living systems and provide new opportunities to investigate redox signaling in neurobiological contexts.

Disclosures: J.D. Lee: None. **Y. Kwon:** None. **Y. Wang:** None. **A. Moghadasi:** None. **A. Berndt:** None.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.01

Topic: A.01. Neurogenesis and Gliogenesis

Support: Schmidt Science Fellows
NIH R01MH133181
NIH R01MH113005

Title: A uniformly processed atlas of human brain development defines cell type-specific maturation trajectories across lifespan

Authors: *S. VENKATESAN[1], P. NANO[3], J. WERNER[2], S. MALAIYA[4], B. HERB[5], A. BHADURI[6], C. COLANTUONI[7], S. A. AMENT[8], J. GILLIS[1];
[2]Physiol. Dept., [1]Univ. of Toronto, Toronto, ON, Canada; [3]UCLA, Los Angeles, CA; [4]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [5]IGS, Univ. of Maryland

Baltimore, Baltimore, MD; [6]Univ. of California Los Angeles, Los Angeles, CA; [7]Johns Hopkins Med. Institutions, Baltimore, MD; [8]Dept. of Psychiatry and Inst. for Genome Sci., U Maryland Sch. of Med., Baltimore, MD

Abstract: Human neurodevelopment is continuous from fetal to postnatal life; yet current single-cell transcriptomic datasets are fragmented across timepoints and analytical frameworks, limiting the reconstruction of coherent cellular trajectories from developmental states to mature cell types. We present a consolidated single-cell and single-nucleus transcriptomic atlas of human brain development from gestational week 6 to adulthood, covering 2.2 million cells from 156 donors across nine studies. All data were reprocessed from raw sequencing reads and annotated within a shared cell-type framework, enabling reliable mapping across the lifespan. Our atlas recovers highly replicable cell types, charting their maturation and cortical layer localization over time. We identify dynamic gene programs predictive of cell-type maturation, validate gene modules tracking known fate transitions, and leverage our atlas' scale to characterize rare populations, including microglia. This resource provides a standardized reference of human brain development and maturation gene modules for future integrative and comparative studies.

Disclosures: S. Venkatesan: None. **P. Nano:** None. **J. Werner:** None. **S. Malaiya:** None. **B. Herb:** None. **A. Bhaduri:** None. **C. Colantuoni:** None. **S.A. Ament:** None. **J. Gillis:** None.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.02

Topic: A.01. Neurogenesis and Gliogenesis

Support: U01 Arlotta

Title: A spatiotemporal single-cell atlas of the developing mouse brain: a resource for studying cell-type specification and spatial organization

Authors: *R. MATHIEU, M. KUNST, L. CHING, J. QUON, D. MCMILLEN, C. S. KIM, N. MARTIN, P. OLSEN, J. NAGRA, S. RANSFORD, N. VALERA CUEVAS, M. VANNESS, J. CAMPOS, A. RUIZ, J. ARIZA TORRES, S. BARTA, M. REDING, O. HELBACK, C. HUANG, E. LIANG, Y. GAO, M. HEWITT, S. C. SEEMAN, S. DANIEL, L. NG, C. M. PAGAN, C. VAN VELTHOVEN, Z. YAO, J. WATERS, H. ZENG;
Allen Inst., Seattle, WA

Abstract: The mammalian brain comprises millions to billions of cells, organized into diverse cell types with distinct spatial distributions and functional properties. In the adult mouse brain, a comprehensive, high-resolution transcriptomic atlas has been generated by integrating whole-brain-scale single-cell RNA sequencing and MERFISH datasets, revealing a strong correspondence between transcriptomic identity and spatial localization. The remarkable

diversity of cell types in the adult brain arises through sequential gene expression changes during neural stem cell maturation and differentiation. While hundreds of molecularly defined cell types have been characterized in the adult brain, their developmental origins and the regulatory programs guiding their formation remain largely undefined. To address this, we applied a set of validated technology platforms to generate a spatially resolved, single-cell atlas of the developing mouse brain with high temporal resolution. Using MERFISH, we captured the full diversity of cell types across postnatal brain development. Through a standardized pipeline leveraging state-of-the-art computational methods, we constructed spatially resolved whole-brain atlases across key postnatal time points from P0 to P28. Analysis of cell-type composition reveals strong reproducibility between paired datasets alongside clear developmental dynamics. Cell types across regions occupy their expected anatomical positions, demonstrating the atlas's power to resolve spatiotemporal cell-type dynamics across the whole brain. As a proof of concept, we focused on the migration of GABAergic interneurons into the isocortex, an essential and poorly understood step in cortical circuit formation. At post-migratory stages, neighborhood enrichment analysis between GABAergic and glutamatergic cell types reveals stereotyped co-localization patterns. Using cross-age alignment within a unified coordinate system, we tracked migratory trajectories of GABAergic cell types during development. Quantification of local cellular diversity highlights that certain GABAergic cell types transition from heterogeneous migratory environments to stereotyped cellular neighborhoods, marking completion of radial migration and laminar integration. Together, this atlas provides a spatiotemporal framework for dissecting the cellular and spatial logic of mammalian brain development, with particular power to address unresolved questions in cell-type specification, maturation, and spatial organization.

Disclosures: R. Mathieu: None. **M. Kunst:** None. **L. Ching:** None. **J. Quon:** None. **D. McMillen:** None. **C.S. Kim:** None. **N. Martin:** None. **P. Olsen:** None. **J. Nagra:** None. **S. Ransford:** None. **N. Valera Cuevas:** None. **M. VanNess:** None. **J. Campos:** None. **A. Ruiz:** None. **J. Ariza Torres:** None. **S. Barta:** None. **M. Reding:** None. **O. Helback:** None. **C. Huang:** None. **E. Liang:** None. **Y. Gao:** None. **M. Hewitt:** None. **S.C. Seeman:** None. **S. Daniel:** None. **L. Ng:** None. **C.M. Pagan:** None. **C. van Velthoven:** None. **Z. Yao:** None. **J. Waters:** None. **H. Zeng:** None.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.03

Topic: A.01. Neurogenesis and Gliogenesis

Support: U01MH130962

Title: A High-Resolution Transcriptomic Atlas of Cell-Type Development in the Mouse Brain

Authors: *Y. GAO[1], C. LEE[5], R. LIU[1], R. MATHIEU[2], M. KUNST[2], N. DEE[7], C. M. PAGAN[3], J. GOLDY[6], A. CHAKKA[4], K. SMITH[1], B. TASIC[3], C. VAN VELTHOVEN[1], Z. YAO[7], H. ZENG[1];
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Abstract: The mammalian brain is highly heterogeneous and develops through a series of temporally regulated events that are essential for its proper function. However, the mechanisms underlying the emergence and maturation of diverse cell types remain incompletely understood. Single-cell RNA sequencing provides a powerful approach for characterizing cellular diversity across development.Here, we present a comprehensive integrated single-cell and single-nucleus transcriptomic atlas of postnatal mouse brain development spanning P0, P1, P2, P4, P5, P6, P7, P8, P10, P12, P14, P16, P20, P28, and P56. The dataset comprises 11.8 million cells and nuclei collected from 10 major brain regions (Isocortex, CTXsp, HPF, OLF, CNU, TH, HY, MB, HB, and CB) and profiled using the 10x Genomics v3, v3.1, v4, and Multiome platforms. Using these data, we developed a computational framework to reconstruct cell-type developmental trajectories, enabling the identification of key developmental transitions and the estimation of cell-type birth timing across brain regions.We further characterized temporal transcriptomic dynamics across subclasses and brain regions, and identified genes associated with lineage bifurcations and other developmental processes. Importantly, the postnatal period encompasses major waves of gliogenesis, circuit maturation, and region-specific neurogenesis. Together, these analyses reveal cell-type-specific developmental programs across the brain and provide a high-resolution resource for investigating mammalian brain development.

Disclosures: Y. Gao: None. **C. Lee:** None. **R. Liu:** None. **R. Mathieu:** None. **M. Kunst:** None. **N. Dee:** None. **C.M. Pagan:** None. **J. Goldy:** None. **A. Chakka:** None. **K. Smith:** None. **B. Tasic:** None. **C. van Velthoven:** None. **Z. Yao:** None. **H. Zeng:** None.

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NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.04

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R00NS111731
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Klingenstein-Simons Fellowship
Ablon Scholar Award
CIRM DISC0-14514
UCLA Zamenhof Scholarship
UCLA Eli and Edythe Broad Center Training Program
Eugene V. Cota-Robles Award

Title: Intrinsic coordination of dynamic molecular signatures shape the human prefrontal cortex

Authors: *P. R. NANO[1], D. JAKLIC[1], J. SOTO[1], J. MIL[1], A. MARTIJA[1], B. WICK[2], M. HAEUSSLER[2], A. BHADURI[1];
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Abstract: The cerebral cortex drives human cognition through the coordinated activity of discrete cortical areas, each harboring specialized molecular, structural and functional characteristics. Central to this organization is the prefrontal cortex (PFC), a hub for executive function that displays disproportionate expansion in humans and selective vulnerability to neurodevelopmental disorders. Previous work has identified a collection of PFC-enriched marker genes with dynamic expression trajectories, and re-analysis of these datasets converge these markers into 18 distinct molecular signatures of spatiotemporal PFC identity. However, the intrinsic gene networks that coordinate these molecular signatures to shape the human PFC remains unclear. Through pooled CRISPR activation screens in human primary cortical tissues, we have evaluated the ability of PFC-enriched transcription factors to intrinsically pattern PFC molecular identity. Our screens identify novel roles for the neurogenesis regulator, YBX1, in the activation of human PFC fate. In parallel screens and knock-down experiments in human cortical organoids, we define how YBX1 acts in concert with other PFC determinants to activate molecular signatures of PFC identity. Our findings support a model in which PFC patterning is orchestrated by cohorts of intrinsic determinants that initiate, potentiate, and modulate PFC gene signatures, conferring robustness to the development of the human PFC.

Disclosures: P.R. Nano: None. **D. Jaklic:** None. **J. Soto:** None. **J. Mil:** None. **A. Martija:** None. **B. Wick:** None. **M. Haeussler:** None. **A. Bhaduri:** None.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.05

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 5R24MH114788-09

Title: A single-cell multi-omic atlas of microglial diversity across the human lifespan

Authors: *S. MALAIYA[1], S. VENKATESAN[2], P. NANO[4], J. WERNER[5], B. HERB[6], C. COLANTUONI[7], A. BHADURI[8], J. GILLIS[3], S. A. AMENT[9];
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Abstract: Microglia seed the developing human brain from the yolk sac as early as gestational week 4 and colonize it to form a self-renewing population that is involved in surveillance, synaptic support and pruning, innate immune defense, myelination and phagocytosis throughout the human lifespan. These roles require transcriptional changes in the cell states that can be captured through single cell RNA sequencing. Here, we integrated scRNA-seq data from 154 donor samples spanning the human lifespan from gestational week 6 to adulthood to create an atlas of microglial diversity in the human brain. We characterized heterogeneous embryonic, early, and mature microglial states and reconstructed their developmental trajectories. Comparisons to scRNA-seq from the human yolk sac enabled us to annotate nascent embryonic microglia that retain yolk sac signatures. Comparisons to scRNA-seq from disease states revealed both similarities and differences in microglial diversity from diseased vs. non-diseased conditions. Analyses of cell-cell communication suggest intercellular signaling mechanisms by which specific microglial subgroups interact with other cell types at each developmental stage. Integration with scATAC-seq from a subset of donors predicted transcriptional regulatory mechanisms. This resource represents one of the largest atlases of microglial diversity across the human lifespan, providing insights into microglial states in both healthy and diseased conditions.

Disclosures: S. Malaiya: None. **S. Venkatesan:** None. **P. Nano:** None. **J. Werner:** None. **B. Herb:** None. **C. Colantuoni:** None. **A. Bhaduri:** None. **J. Gillis:** None. **S.A. Ament:** None.

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NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.06

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIRM Training Grant: EDUC4-12772

Title: Zeb1 drives the neurogenesis-to-gliogenesis transition and controls oligodendrocyte specification.

Authors: *C. GONZALEZ[1], J. LIU[2], R. R. QIU[3], Q. LU[4];
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Med., Bechman Res. Inst, City Hope, Duarte, CA; [4]Dept. of Developmental and Stem Cell Biol., Beckman Res. Inst. of the City of Hope, Duarte, CA

Abstract: During brain development, the balance between neurogenesis and gliogenesis is tightly regulated by complex transcriptional networks. ZEB1, a zinc-finger E-box-binding transcription factor, is known for its roles in epithelial-mesenchymal transition (EMT) and neural differentiation and migration; however, its functions in gliogenesis and oligodendrocyte lineage specification remain poorly understood. Here, we show that ZEB1 is enriched in oligodendrocyte progenitor cells (OPCs) during the neurogenesis-to-gliogenesis transition. Single-cell RNA sequencing of embryonic cortical neural progenitor cells revealed increased Zeb1 expression in the OPC population from E15.5 to E18.5. Immunohistochemical analyses further confirmed the temporal and spatial expression of ZEB1, demonstrating co-localization with glial and OPC markers, including SOX9, PDGFRα, and OLIG2, but not with neuronal markers. Functional studies using in utero electroporation showed that Zeb1 overexpression at the neurogenic stage (E13.5) retained transfected cells within progenitor zones, promoted a gliogenic fate marked by SOX9 expression, and induced basal radial glia-like morphology. In contrast, Zeb1 knockout resulted in a significant reduction of OLIG2-positive oligodendrocyte lineage cells at embryonic (E18.5) and postnatal (P7 and P28) stages without disrupting cortical neuronal layering. Collectively, these findings identify Zeb1 as a key regulator of the neurogenesis-to-gliogenesis transition and oligodendrocyte lineage specification during brain development.

Disclosures: C. Gonzalez: None. **J. Liu:** None. **R.R. Qiu:** None. **Q. Lu:** None.

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NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.07

Topic: A.01. Neurogenesis and Gliogenesis

Support: HHMI
NIH HD27056
NIH 5-T32-GM149387

Title: Eyeless (Pax6) operates with progenitor temporal transcription factor programs to establish distinct neuronal classes

Authors: *G. MORALES CHAYA, L. MANNING, C. Q. DOE;
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Abstract: Complex brain functions rely on the precise formation of circuits from multiple neuronal types. Each type first acquires a unique transcriptional profile that ultimately defines its morphology, connectivity, and physiology. How distinct molecular identities are assigned to individual neuronal types from a limited pool of progenitor cells remains poorly understood.

During development, individual neural progenitor lineages generate multiple distinct neuron classes over time. Progenitors of the mammalian neocortex, known as radial glial cells (RGCs), produce intermediate progenitors that amplify the progenitor pool and give rise to neurons in an inside-out manner — early-born neurons settle in deep cortical layers while late-born neurons occupy superficial ones. RGCs undergo transcriptional changes that facilitate this temporal diversification, and lineage-specific transcription factors are repurposed across developmental time to generate different cell types. Yet the molecular mechanism by which the same factor specifies distinct identities remains unclear.
To investigate this, we use *Drosophila* Type 2 neuroblasts (T2NBs) as a genetically tractable model. Like RGCs, T2NBs divide to produce intermediate progenitors (INPs) that self-renew and amplify neuronal output. T2NBs generate ~160 molecularly distinct cell types, most innervating the central complex — a brain region conserved across insects and required for sensorimotor integration. T2NBs and INPs each undergo independent temporal transcription factor (TTF) cascades — several with mammalian orthologs in cortical progenitors (e.g., Eyeless/Pax6) — and many of the resulting neuron types have been birth-dated, directly linking TTF expression windows to neuronal identity.
The INP TTF Eyeless (Ey) exemplifies this conservation: Ey is expressed in old INPs throughout lineage development, yet specifies distinct neuron types — including EPG neurons from early T2NBs and PFR neurons from late T2NBs — demonstrating that the same INP TTF produces different outcomes depending on the age of its parent T2NB. We hypothesize that as T2NBs age, they progressively remodel their chromatin landscape, causing Ey to access different genomic targets in early- versus late-born INPs. To test this, we map Ey genomic binding via CUT&RUN and chromatin accessibility via ATAC-seq in INTACT-purified Ey+ INPs isolated from early and late T2NBs, and functionally test whether Ey targets act as fate determinants for distinct neuron types. Together, this work reveals how a single transcription factor is repurposed across development to build neuronal diversity.

Disclosures: G. Morales Chaya: None. **L. Manning:** None. **C.Q. Doe:** None.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.08

Topic: A.01. Neurogenesis and Gliogenesis

Support: 1R01MH134799-01

Title: Neuronal diversification in the developing mouse spinal cord

Authors: *C. RIVERA[1], C.-W. ZENG[1], H. POLDSAM[1], N. PIAZZA[2,3], J. E. JOHNSON[4], S. CHOI[5], A.-H. POOL[6], H. C. LAI[7];
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Med. Ctr., Dallas, TX; [6]Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [7]UT Southwestern Med., Dallas, TX

Abstract: During embryogenesis, transcription factors combinatorially define 11 discrete progenitor domains that control the differentiation of defined cell types in the spinal cord. However, the relationship between developing progenitor domains and molecular features in the adult spinal cord is not clearly defined. Our goal is to construct molecular, and anatomical atlases to help us understand the process through which embryonic progenitor domains give way to the vast heterogeneity found in the adult spinal cord. Using the 10x Multiome platform, we have generated gene expression, and open chromatin region maps of three representative stages E11.5 (embryonic timepoint), P4 (early postnatal timepoint) and P56 (adult timepoint) along the rostral - caudal axis. We have also densely profiled the gene expression of neural tube development, sampling daily from E10.5 to P0 to follow the cell types resulting from each progenitor domain. In an orthogonal approach, we have traced the lineage of the different progenitor domains using spinal cord-Cre/FLPo mouse lines combined with Xenium spatial transcriptomics to identify their final cell types. These two orthogonal approaches will provide a clearer understanding of the relationship between developmental and mature cell types and their structural organization.

Disclosures: C. Rivera: None. **C. Zeng:** None. **H. Poldsam:** None. **N. Piazza:** None. **J.E. Johnson:** None. **S. Choi:** None. **A. Pool:** None. **H.C. Lai:** None.

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NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

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Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO45.09

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIMH Grant R01MH135403
NINDS Grant R01NS128087

Title: Rapid and efficient oligodendrocyte differentiation from human pluripotent stem cells via dual inhibition of BMP and Notch signaling.

Authors: *A. EVANGELISTI[1,2], S. PHILLIPS[2], J. JUNGVERDORBEN[2], R. WALSH[2], Y. WU[2], V. BOCCHI[2], T. ZHOU[2], L. STUDER[2];
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Abstract: The protracted timing required for oligodendrocyte differentiation from human pluripotent stem cells (hPSCs) has limited their use in disease modeling, drug screening, and cell therapy. In particular, the signals that drive oligodendrocyte specification and maturation after neural induction and ventral patterning remain poorly understood. Here, we present a protocol to derive human oligodendrocytes from hPSCs that is based solely on extrinsic cues, and we

identify dual inhibition of BMP and Notch signaling as critical drivers of oligodendrocyte commitment and maturation. By day 42 of differentiation, up to 70% of the cells are positive for the oligodendrocyte marker O4, with minimal astrocyte contamination, and show robust expression of mature myelin markers including MBP, MOG, and MAG. These hPSC-derived oligodendrocytes closely match the molecular identity of primary fetal human oligodendrocytes as assessed by single-cell RNA sequencing and are functional as shown by *in vitro* myelination assays. In addition to the rapid generation of myelinating oligodendrocytes, the new protocol can be modularly adapted for the efficient production of PDGFRα+ oligodendrocyte precursors or mixed glial populations containing AQP4+ astrocytes, thereby providing a cellular toolbox for the study of human glial lineages in translational applications.

Disclosures: A. Evangelisti: None. **S. Phillips:** None. **J. Jungverdorben:** None. **R. Walsh:** None. **Y. Wu:** None. **V. Bocchi:** None. **T. Zhou:** None. **L. Studer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder and scientific advisor of BlueRock Therapeutics, Co-founder and scientific advisor of DaCapo Brain Science.

Nanosymposium

NANO45: Single-Cell and Spatial Atlases of Neural Development: From Resource Generation to Mechanism

Location: WCC Rm 207A

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Presentation Number: NANO45.10

Topic: A.01. Neurogenesis and Gliogenesis

Support: CIHR Grant
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Medicine by Design postdoctoral fellowship
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Stem cell network
Brain Canada

Title: Human pluripotent stem cell-derived 3D co-culture models help identify determinants for microglial invasion and residency in the brain

Authors: *A. TIAN[1], A. BHATTACHARYA[1,2], F. SUN[1,2], S. VENKATESAN[3,1], W. CHOI[1,2], M. AHMED[1], Y. LI[1,2], J. MUFFAT[1,2];
[1]The Hosp. for Sick Children, Toronto, ON, Canada; [2]Dept. of Mol. Genet., [3]Dept. of Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Microglia are brain-resident macrophages that survey their surroundings and orchestrate potent responses to injury. Emerging from the yolk sac, microglia invade the fetal brain and establish lifelong residence. Brain residency is essential for microglia to acquire their

functional form and reciprocally crucial for brain development. Little is known about the mechanisms underlying these coordinated developmental processes. To advance our understanding of microglia-brain co-development, support disease-modeling efforts and improve microglia transplantation for cell therapy, we have established human pluripotent stem cell-derived 3D microglia co-culture models. We observed microglial ramification, surveillance behavior and signature gene upregulation upon their co-culture with neural-precursor-differentiated neurons and glial cells. Single cell RNAseq identified microglia, neurons, astrocytes and oligodendrocytes in the co-culture with predicted age around GW20. Communication network analysis revealed strong astrocyte-microglia interactions but comparatively weak neuron-microglia interactions. To experimentally assess the cellular and molecular requirements of individual brain cell types for microglia brain residence, we developed a deterministic system of defined cell type assemblies between NGN2-induced neurogenic cultures and purified astrogenic cultures. We found astrogenic cultures, but not NGN2-induced neurogenic cultures, possess the machinery required for microglia entry, ramification and survival. The astrocyte-microglia co-culture is self-sustainable and responsive to inflammatory stimuli. Intersections of inferred ligand-receptor pairs and differentially expressed genes between astrogenic cultures and NGN2-induced neurogenic cultures helped us further identify key astrocyte-microglia communication genes such as CSF1 (Colony Stimulating Factor 1). We found that genetic ablation of CSF1 in astrogenic cultures prevented microglia integration and forced expression of CSF1 in NGN2-induced neurogenic cultures provided permissiveness to microglia invasion. Finally, we noted that astrocyte-microglia co-transplantation facilitated microglial residence. Together, we established microglial 3D co-culture models and uncovered astrocytes-microglia interactions that are required for microglial invasions and brain residence. Our findings highlighted the potential of using astrocytes as chaperones to facilitate microglia brain engraftment.

Disclosures: A. Tian: None. **A. Bhattacharya:** None. **F. Sun:** None. **S. Venkatesan:** None. **W. Choi:** None. **M. Ahmed:** None. **Y. Li:** None. **J. Muffat:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.01

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

Support: FWF Grant W1232

Title: [^{3}H]PZ-II-028, a novel Radioligand Targeting the $GABA_A$Receptor α^+/β^-Interface

Authors: *P. SCHOLZE[1], D. SCHNALZER[2], P. WELLENDORPH[3], M. SCHNÜRCH[2], M. ERNST[1];
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TU Wien, Wien, Austria; [3]Dept. of Drug Design and Pharmacol., Univ. of Copenhagen, Kobenhavn O, Denmark

Abstract: $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the mammalian brain, exist as different receptor subtypes and are the target of many clinically important drugs. The most prominent receptor subtype is αxβxγ2. GABA binds at the extracellular β^+/α^- region, while benzodiazepines interact with the α^+/γ^-interface. Radiolabeled compounds are indispensable tools to further study those receptors, map their distribution and screen for novel compounds. However, currently available radioligands and radiotracers are largely restricted to a limited number of binding sites, such as [^{3}H]muscimol binding to the canonical GABA (β^+/α-) site, [^{35}S]TBPS and [^{3}H]EBOB binding to the channel pore, and [^{3}H]diazepam, [^{3}H]flunitrazepam, [^{3}H]Ro 15-4513, and [^{3}H]Ro 15-1788 that interact with the high affinity benzodiazepine site. In the present study we present a novel compound from the pyrazoloquinolinone family, which exhibits a dual mode of action, acting as functionally neutral ligand at the benzodiazepine site while serving as strong positive allosteric modulators at the extracellular α^+/β^- interface. This compound called [^{3}H]PZ-II-028 was synthesized as a tritium-labeled radioligand and subsequently evaluated in autoradiography and radioligand binding assays employing heterologously expressed $GABA_A$ receptors and native rat brain tissue. Our studies show that this novel radioligand binds with high affinity in the pM range to the high affinity benzodiazepine site of γ2-containing receptors. In the high nM range [^{3}H]PZ-II-028 in addition labels α1β1-, while sparing α1β2/3 receptors, consistent with the published electrophysiology. This binding can be dose-dependently displaced by other pyrazoloquinolinones with similar structure. Binding is reduced in receptors with mutations at the putative drug binding site, confirming interaction at the α^+/β^- interface. This radioligand can now be used to further investigate β1- containing $GABA_A$ receptors, since the α^+/β^- interface is present in a broader range of GABAA receptor assemblies than the classical benzodiazepine binding site. Radioligands directed at this site could therefore expand the scope of receptor populations available for investigation by enabling the characterization of rare or previously inaccessible receptor configurations beyond conventional benzodiazepine-sensitive assemblies.

Disclosures: P. Scholze: None. **D. Schnalzer:** None. **P. Wellendorph:** None. **M. Schnürch:** None. **M. ernst:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.02

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

Title: Neurotransmission N-Glycosylation Profiles in Dorsolateral Prefrontal Cortex of Individuals with Major Depression and Bipolar Disorder

Authors: *G. PRESTON;
Icahn Sch. of Med. at Mount Sinai, Bronx, NY

Abstract: Mood disorders represent a broad and heterogenous group of psychopathologies characterized generally by disruptions in an individual's emotional state. Several pathogenic mechanisms have been implicated in mood disorders, including neurodevelopmental abnormalities, metabolic dysregulation, and epigenetic modification. Recently, dysregulation in neurotransmission, specifically in excitatory and inhibitory neurotransmission has been the focus of much research. While genetic variants in neurotransmission have been well reported on, relatively little attention has been paid to post-translational modification. Protein N-glycosylation is the most expansive post-translational modification in eukaryotes, involving the ligation and subsequent modification of complex carbohydrate chains onto asparagine residues of nascent polypeptides. Neurotransmission in the brain is a complex cellular process involving hundreds of protein species. Alterations to the number, distribution, size, and composition of bulky post-translational modification moieties such as N-glycans, has the potential to impact neurotransmitter receptor activity in complex and potentially profound ways. While it is indeed well established that altered cell surface N-glycosylation in the brain is associated with psychopathology, to date, studies have been restricted to serum and cerebrospinal fluid rather than postmortem tissues. Here we investigate the potential role of site-specific alterations in glycan abundances and composition associated with mood disorders by performing untargeted glycoproteomics analysis on postmortem dorsolateral prefrontal cortex samples from 3 individuals with major depressive disorder, 6 individuals with bipolar disorder (3 who were depressed at time of death, and 3 who were manic at time of death), and 3 non-psychiatric controls. We characterize the site-specific glycan abundances and compositions across numerous cell surface proteins involved in neurotransmission in non-psychiatric controls, including both glutamate and GABA receptors, and voltage gated calcium ion channels. We also identified altered glycan abundances at several of these sites associated with mood disorders generally, major depression, and bipolar disorder. We also identified site specific alterations in glycan abundances associated with either unipolar or bipolar disorder specifically, as well as with bipolar mania. These data shed new light on the putative role of N-glycosylation alterations in the pathobiology of mood disorders, as well as potential novel therapeutic strategies aimed at modifying altered N-glycosylation in affected individuals.

Disclosures: G. Preston: None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

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Presentation Number: NANO46.03

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

Support: NIH grant 1R01MH114908-01
University of Pittsburgh Pharmacology and Chemical Biology Fellowship

(William C. deGroat Neuropharmacology Departmental Fellowship)
University of Pittsburgh School of Medicine Research Funds

Title: Sex-specific differences in cortical gene and protein expression following chronic diazepam treatment

Authors: *J. L. NUWER[1], C. CHAPMAN[1], M. C. WESTON[2], M. L. SENEY[3], M. L. MACDONALD[3], S. T. WEINTRAUB[4], T. C. JACOB[1];
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Abstract: Benzodiazepines (BZs) are among the most widely prescribed psychotropic drugs for their anxiolytic, sedative, and anticonvulsant effects, which are mediated through positive allosteric modulation of GABA type A receptors ($GABA_ARs$). Safe clinical use is limited by drug tolerance and a hyperexcitable withdrawal syndrome characterized by neuronal excitation/inhibition (E/I) imbalance. Despite recommendations for short-term use, BZs are routinely prescribed beyond these timeframes, yet the molecular mechanisms driving tolerance remain elusive. Critically, while women are prescribed BZs at approximately 1.5-2x the rate of men, current mechanistic understanding relies predominantly on *in vitro* and male-only *in vivo* findings. We previously showed in male mice that 7-day (7d) treatment with the BZ diazepam (DZP) redistributes extrasynaptic BZ-insensitive $GABA_ARs$ to synapses and upregulates the total and synaptic protein levels of excitatory glutamate NMDA receptors (NMDARs). Functionally, these changes shifted the overall E/I balance toward excitation both by reducing BZ-sensitive phasic inhibition and concurrently lowering tonic inhibition and by enhancing NMDAR activity. Quantitative proteomics showed an upregulation of kinases that regulate NMDAR and $GABA_AR$ trafficking and function, synaptogenesis and remodeling, excitatory LTP, and drug tolerance. Here, we aim to confirm and expand upon these findings in both male and female mice using a combination of RT-qPCR, biochemical, and proteomic analysis. Two-way ANOVAs of RT-qPCR data reveal 7d DZP treatment reduces mRNA levels of *gabrg2* and *gabra1* in females only. *Mapk3* RNA was increased by DZP treatment, and overall expression was lower in females (main effects). While treatment did not alter RNA levels of *gabra5* and *grin1*, these genes were expressed at lower levels in females compared to males. Biochemical analysis reveals 7d DZP treatment reduces total protein levels of the inhibitory postsynaptic scaffold gephyrin in females but not males, consistent with our prior all-male cohort. Preliminary analysis of total protein levels suggests 7d DZP treatment increases GluN1 and CREB in males only and PSD95 in both males and females. Membrane fractionation and proteomic studies are ongoing to determine the sex-specific effects of 7d DZP on expression levels of excitatory and inhibitory synaptic proteins and kinases. Uncovering the mechanisms that drive tolerance, especially in females, will aid in mitigating BZ-induced neuroadaptations and promoting the development of novel BZs with reduced risks for all patients.

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Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

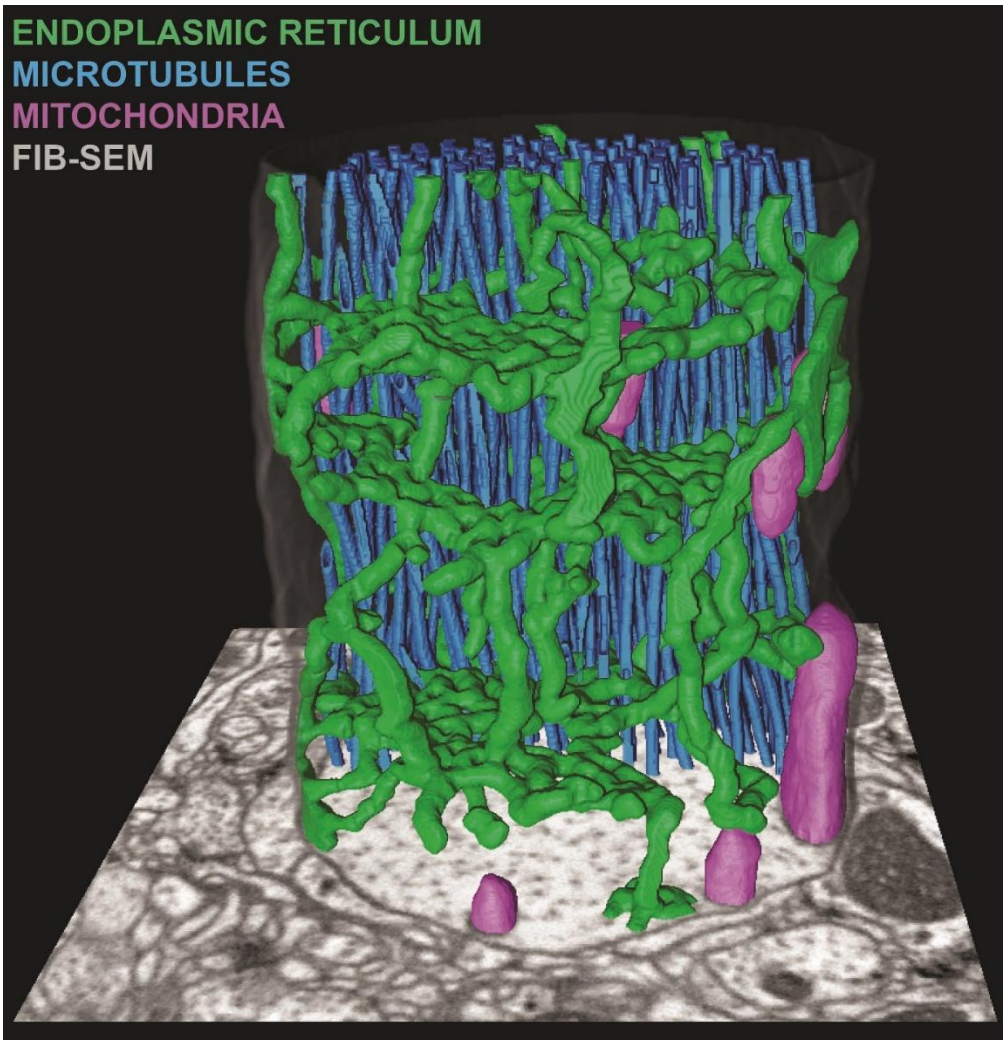
Presentation Number: NANO46.04

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

Title: The regular distribution of endoplasmic reticulum-plasma membrane contact sites in dendrites, facilitates the long-distance integration of Ca^{2+} signals.

Authors: *L. BENEDETTI[1], R. FAN[5], A. WEIGEL[7], A. MOORE[2], P. R. HOULIHAN[3], M. KITTISOPIKUL[1], P. M. HUBBARD[8], S. PANG[9], C. XU[9], H. HESS[10], S. SAALFELD[11], V. RANGARAJU[6], D. E. CLAPHAM[4], P. V. DE CAMILLI[12], T. A. RYAN[13], J. LIPPINCOTT-SCHWARTZ[14];
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Abstract: The propagation of intracellular signals over long-distances presents a unique challenge in neurons. While electrical conduction along the plasma membrane (PM) is well-studied, how spatially and temporally confined intracellular messengers, like Ca^{2+}, can elicit responses hundreds of microns from locally stimulated dendritic spines remains a mystery. The endoplasmic reticulum (ER) is ideally suited to overcome these obstacles. The ER can interface with the membranes of organelles (contact sites) facilitating confined intracellular reactions. Its continuity can potentially support the propagation of messengers over the entirety of the cell. Given the narrow caliber of ER tubules, diffraction-limited microscopy has prevented the field from appreciating the organization of the ER in dendrites. Using super-resolution microscopy and volumetric electron micrograph reconstruction, we discovered periodically spaced contact sites (1 υm) between the ER and PM. We determined that the Huntington disease-related protein Junctophilin-3 coordinates contact site formation by linking ER Ca^{2+} channels and voltage-gated calcium channels on the PM. These channels enable precise control of Ca^{2+} release and uptake from the ER in response to extracellular Ca^{2+} entry triggered by spine stimulation. These ER-PM contacts expand and change their molecular composition in response to elevated PM excitability. Relevant to intracellular signaling, we found ER-PM contacts are preferred sites for initiating and propagating CaMKII-dependent signaling, a Ca^{2+}-activated kinase essential for neuronal plasticity. Our results describe a novel ER organization harboring periodic contact sites with the PM in dendrites that helps propagate local Ca^{2+} signals from individually stimulated spines.



Disclosures: L. Benedetti: None. **R. Fan:** None. **A. Weigel:** None. **A. Moore:** None. **P.R. Houlihan:** None. **M. Kittisopikul:** None. **P.M. Hubbard:** None. **S. Pang:** None. **C. Xu:** None. **H. Hess:** None. **S. Saalfeld:** None. **V. Rangaraju:** None. **D.E. Clapham:** None. **P.V. De Camilli:** None. **T.A. Ryan:** None. **J. Lippincott-Schwartz:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.05

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

Title: Mapping axonal cytoskeletal deficits in Batten disease

Authors: *A. GANGULY;
Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Batten disease is an inherited, juvenile onset, fatal neurodegenerative disease primarily associated with mutations in the *Cln3* gene, a protein expressed on the late-endosomal/lysosomal membrane. While Cln3 has been implicated in regulation of autophagy, lysosomal lipid degradation and endocytosis, it is not understood how loss of Cln3 contributes to early behavioral deficits, such as anxiety, epileptic episodes, and impaired cognitive learning. *In vivo* recordings from murine models show increased neuronal excitability, network hyperactivity, and epileptiform activity. These changes in neuronal firing precede the onset of lysosomal dysfunction and are not resolved by drugs targeting lysosomal storage dysfunction. Since changes in intrinsic neuronal excitability can lead to the onset of epileptiform activity, we hypothesize that changes in the intrinsic excitability of *Cln3* deficient neurons may underly the onset of early neuronal dysfunction. The axon-initial-segment (AIS) is an axonal region critical for action potential initiation and for shaping the neuron's firing properties. Induction of neuronal activity, for instance during behavioral learning, results in homeostatic changes in AIS size. Our studies with primary hippocampal neurons from *Cln3* knockout mice indicate that Cln3 loss results in a shorter and a more proximal location of the AIS along the axon, when compared to wild-type neurons. This mimics the AIS size and position in neurons with higher intrinsic excitability as seen in murine models of epilepsy. We also observe an impairment in activity induced homeostatic plasticity of the AIS in *Cln3* deficient neurons. Our experiments reveal that this AIS phenotype is primarily driven by higher lysosome numbers and a higher expression of lysosomal calcium channels. We also show that the inhibition of calcium efflux via lysosome specific calcium channels can rescue defects in AIS plasticity. Thus, our work identifies a possible role for lysosomal calcium channels in regulating neuronal excitability upon the loss of Cln3.

Disclosures: A. Ganguly: None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.06

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

Support: NSFC Grant 82371233
NSFC Grant 81450064

Title: Proton-Activated Chloride (PAC) Channels Maintain normal nociceptive processing Through the suppression of central amygdala GABAergic Neurons

Authors: F. QINGKE[1], Y. XU[1], G. JIE[1], R. ZHANG[2,3], Z. ZHANG[1,4], ***Q. TANG**[1,4];
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Normal Univ. Jiangning Campus, Nanjing, China; [3]Univ. of California San Diego, San Diego, CA; [4]Sch. of Anesthesiol., Xuzhou Med. Univ., Xuzhou, China

Abstract: Physiological pain perception (PPP) is essential for survival, enabling the detection of noxious stimuli and protecting the body from injury, yet the neuronal mechanisms underlying the maintenance of normal pain perception remain poorly understood. The central amygdala (CeA) is a key regulator of nociceptive processing; the molecular and cellular mechanisms within CeA that regulate PPP have not been fully elucidated. Here we discovered a proton-activated chloride (PAC) channel as a critical regulator of normal pain perception in mice. We found that PAC was highly expressed in CeA GABAergic (CeA^{GABA}) neurons. By utilizing global PAC knockout (PAC-KO) mice and selective PAC knockdown in CeA^{GABA} neurons, we demonstrate that the lack of PAC function mostly abolishes PPP responses to thermal (cold and heat) and mechanical (Von Frey and Pinck) stimuli. Whole-cell recordings from acute brain slices revealed that PAC-gene deficiency significantly enhanced the intrinsic excitability of CeA^{GABA} neurons. Importantly, selective re-expression of PAC channels in CeA^{GABA} neurons restored the PPP and the neuronal. Furthermore, a PAC channel blocker, DIDs, substantially reduced nociception in wild-type mice and increased the excitability of GABAergic neurons. These findings identified PAC channels as essential maintenance/regulators of physiological pain perception through the suppression of CeA GABAergic neuronal excitability. Our study thus uncovers a previously unrecognized CeA-PAC-dependent mechanism in the maintenance of normal pain sensation and provides new insights into the neuronal basis of physiological pain perception.

Disclosures: F. Qingke: None. **Y. xu:** None. **G. jie:** None. **R. Zhang:** None. **Z. Zhang:** None. **Q. Tang:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.07

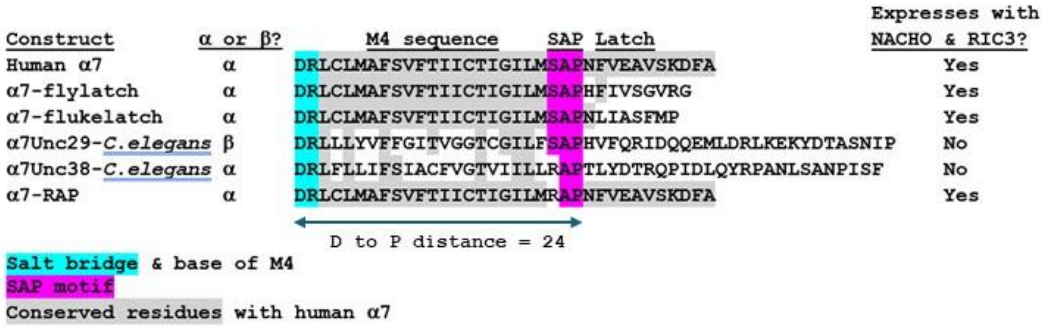
Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Conservation of the humana7 SAP motif across species and nicotinic receptor sub-units

Authors: *R. H. LORING[1], J. HIMMELSTEIN[1], A. IRAQUI[1], F. PATEL[1], J. PEDERSEN[2], D. S. LARHAMMAR[3];
[1]Northeastern Univ., Boston, MA; [2]Neurosci., Uppsala, ; [3]Uppsala University, Dept Neuroscience/Unit Pharmacol, Uppsala.

Abstract: Background: How surface receptors fold and assemble is not understood even though they bind neurotransmitters and a wide variety of drugs. Improperly folded receptors can lead to epilepsy and are implicated in other neurological conditions such as Alzheimer's disease and schizophrenia. α7 nicotinic receptor (Hα7 nAChR, including the α7 nAChR-FamA fusion protein variant) is unique among human nicotinic receptor subunits to have transmembrane 4 (M4)

terminate in an SAP (Serine-Alanine-Proline) motif before a helical C-terminal called the latch. However, the SAP motif is highly conserved among both α7 nAChR homologs and other nicotinic subunits in multiple species. For instance, in *C. elegans* the SAP motif is found in 7 of all known 27 nicotinic subunits (including both αs and βs) and SAP variants (e.g. RAP, TAP) are found in another 11 (In *D. melanogaster*, SAP variants are in 90% of subunits). The conserved SAP motif implies a possible mechanistic role. **Hypothesis:** Hα7 nAChRs require chaperones NACHO and RIC3 for proper folding and assembly and we hypothesized that they may be required to fold subunits with SAP motifs in other species as well. We previously found that NACHO and RIC3 fold Hα7 chimeric proteins with the latch replaced with that of flies or liver flukes. In these experiments, we tested whether human NACHO and RIC3 can fold α7 chimeras with the entire M4 domain and C-terminal replaced with those of other species. **Methods:** α7 folding was indirectly measured in BOSC23 cells using fluorescent α-bungarotoxin binding after transfection as an indication of surface receptor expression. **Results:** We found that Hα7-M4 chimeras from C. elegans Unc29 (SAP) and Unc38 (RAP) do not express with NACHO and RIC3. The RAP motif in Unc38 is not the cause, as Hα7-nAChR with a S489R (RAP) mutation expresses well. Further experiments will determine if incompatibility between mutant M4 and Hα7 M2 and M3 causes failure to express or if the length of the latch is an issue. NACHO and RIC3 co-evolve with nicotinic receptors in individual species. Thus, changes in chaperone function across species may also be involved.



Disclosures: R.H. Loring: None. **J. Himmelstein:** None. **A. Iraqui:** None. **F. Patel:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.08

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

Support: NIH Intramural Research Program
ZIA MH002946-13

Title: SNX3 and SNX17 Regulate Bidirectional Trafficking of Neuronal Glutamate Transporter, EAAT3

Authors: *S. RADHAKRISHNAN[1], O. PEMBERTON[1], S. GHODRATI[2,1], S. SHEPARD[1], S. G. AMARA[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: The neuronal excitatory amino acid transporter 3 (EAAT3) is a plasma membrane transporter essential for glutamate clearance, preventing synaptic spillover and modulating glutamatergic signaling. EAAT3 mutations are associated with several neuropsychiatric disorders, including schizophrenia and obsessive-compulsive disorder. EAAT3 surface expression is dynamically regulated by trafficking to and from the plasma membrane, and drugs such as amphetamines can drive its internalization, altering glutamate signaling. A C-terminal ^{504}VNGGF^{508} motif is critical for the somatodendritic targeting of EAAT3 in hippocampal neurons and is required for amphetamine-mediated internalization, implicating it as a key regulatory hub. To identify endogenous interactors of EAAT3, we used proximity labeling (TurboID) coupled with mass spectrometry in N2A cells and primary cortical neurons expressing TurboID-EAAT3 under a CMV promoter or synapsin promoter, respectively. This tag biotinylates proteins within a 10nm radius of EAAT3 and allowed us to identify two sorting nexins: SNX3, a component of the retromer pathway, and SNX17, a component of the retriever pathway, suggesting EAAT3 is sorted through both pathways. Interactions between EAAT3 and both sorting nexins were confirmed by proximity ligation assay (PLA) and confocal microscopy in N2A cells and primary hippocampal neurons. Super-resolution STED microscopy localized the SNX3-EAAT3 interaction to the early endosomal membrane and confirmed colocalization of endogenous EAAT3 with both SNX3 and SNX17 in hippocampal neuron dendrites. Functional studies using siRNA-mediated knockdown revealed opposing roles for the two sorting nexins: loss of SNX3 increased EAAT3 surface expression, while loss of SNX17 decreased it, demonstrating that SNX3 and SNX17 bidirectionally regulate EAAT3 membrane localization. Apilimod-mediated PIKFYVE inhibition increased EAAT3 endosomal retention and reduced surface expression, supporting SNX3's role in retrograde trafficking. Co-immunoprecipitation confirmed that EAAT3 binds endogenous SNX17. PLA experiments also showed that mutation of the C-terminal VNGGF motif reduced EAAT3 interactions with SNX3 and the WASH complex protein WashC2, while acute disruption of this motif using a TAT-interfering peptide paradoxically increased these interactions, suggesting competitive, motif-dependent regulation at the C-terminus. Together, these findings reveal that the constitutive trafficking of EAAT3 is governed by a bidirectional sorting nexin switch at its C-terminus, with implications for understanding how amphetamines regulate glutamatergic signaling.

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

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO46.09

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

Support: ZIA HD008914
ZIA HD008869

Title: Neto-a gates presynaptic kainate receptors to control neurotransmitter release in vivo

Authors: *T. HAN[1], W.-C. HSIEH[2], R. VICIDOMINI[3], Z. LI[4], M. SERPE[5];
[1]NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Bethesda, MD; [2], Eunice Kennedy Shiver Natl. Inst. of Child Hlth. and Human Develop., [3]Eunice Kennedy Shiver Natl. Inst. of Child Hlth. and Human Develop., [4]Natl. Inst. of Mental Hlth., [5]Natl. Inst. of Child Hlth. and Human Develop., NIH, Bethesda, MD

Abstract: Auxiliary proteins are established modulators of glutamate receptor distribution and function, yet how these activities shape synaptic strength and autoreceptor-mediated facilitation of neurotransmitter release remain unclear. Here, we demonstrate that *Drosophila* Neto-α governs the activity of presynaptic KaiR1D kainate autoreceptors in motor neurons to control neurotransmitter release at the larval neuromuscular junction. Loss of either KaiR1D or Neto-α reduces basal neurotransmission, and KaiR1D overexpression fails to restore synaptic output in the absence of Neto-α, revealing an obligate functional dependence on this auxiliary protein. Using genetics, heterologous reconstitution, and outside-out patch recordings with rapid agonist application, we show that Neto-α both promotes presynaptic accumulation of KaiR1D and modulates its gating kinetics. Specifically, Neto-α promotes KaiR1D delivery to axonal compartments and favors receptor enrichment near presynaptic sites. In addition, Neto-α reshapes KaiR1D channel gating by limiting rapid desensitization, enhancing receptor-mediated charge transfer, and modifying toxin sensitivity. To distinguish between Neto-dependent receptor localization and gating modulation, we engineered Neto variants that selectively uncouple these functions. Strikingly, a ΔCUB1-Neto-α variant that supports axonal distribution of KaiR1D but fails to regulate gating kinetics does not rescue basal neurotransmission, demonstrating that Neto-dependent trafficking alone is insufficient to sustain synaptic output. Instead, Neto-α enhances presynaptic charge transfer and likely increases KaiR1D-mediated Ca^{2+} influx, thereby facilitating neurotransmitter release. Together, these findings define a modular role for Neto-α in coordinating receptor gating with presynaptic distribution and establish Neto proteins as essential determinants of synaptic strength *in vivo*.

Disclosures: T. Han: None. **W. Hsieh:** None. **R. Vicidomini:** None. **Z. Li:** None. **M. Serpe:** None.

Nanosymposium

NANO46: Molecular Physiology of Ligand-Gated Receptors and Ion Channels

Location: WCC Rm 140

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Presentation Number: NANO46.10

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

Support: NIH 5R35NS132248

Title: Functional deficits and pharmacological rescue for Grin1 variants

Authors: *G. K. POPESCU;
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Abstract: NMDA receptors are tetramers composed of two obligatory GluN1 subunits and two GluN2 subunits, of which four types (A-D) are expressed differentially. These polypeptides are encoded by *Grin1* and *Grin2A-D* genes, respectively. Variations in the *Grin1* gene sequence produce neurodevelopmental disorders with an incidence of 5.45 per 100,000 births, and often encompass symptoms previously associated with epilepsy, intellectual disabilities, and movement disorders. Of the more than 500 variants identified to date, only a handful have been characterized in sufficient detail to warrant therapeutic recommendations. Specifically, several variations at the GluN1 Y647 residue are pathogenic, including Y/C, Y/H, and Y/S. Patients with these variants have severe developmental delay, acquired microcephaly, extensive bilateral polymicrogyria, and seizure activity from epileptic encephalopathies. We used single-molecule electrophysiology, kinetic modeling, and simulations to identify the mechanisms by which these three variants, when co-expressed with GluN2A in HEK-293 cells, modify the gating reaction of NMDA receptors. We found that all three variants had a markedly lower open probability, specifically due to much longer mean closed durations. Further, we found that the synthetic positive allosteric modulator GNE-9278 (50 μM) increased the open probability of these variants to values approaching those observed for wild-type receptors in the absence of a modulator. Based on kinetic analyses and modeling of these data, we propose a quantitative mechanism by which GNE-9278 restores gating and conductance deficits in the variants we examined. Therefore, results suggest that GNE-9278 may represent a promising pharmacologic intervention for patients who carry these variants.

Disclosures: G.K. Popescu: None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.01

Topic: C.06. Neuromuscular Diseases

Support: 2R01NS114510-06A1

Title: An Embryonic Genetic Program Safeguards Breathing in ALS

Authors: *R. LOPEZ DE BOER, P. PHILIPPIDOU;
Case Western Reserve Univ. Dept. of Neurosciences, Cleveland, OH

Abstract: Respiratory failure is the leading cause of death in ALS, yet the molecular pathways that lead to respiratory dysfunction throughout disease progression are not well understood. At end stages of the disease, contraction of the diaphragm muscle is impaired, largely due to the loss of phrenic motor neurons (MNs), which provide the only motor innervation to the diaphragm. Much of our current understanding of ALS disease mechanisms comes from the study of limb MNs and locomotor circuits. However, these findings may not extend to phrenic MNs, as they are molecularly and genetically distinct and embedded into non-overlapping motor circuits. Our preliminary data using the SOD1(G93A) mouse model of ALS indicate that breathing dysfunction arises at late stages of ALS progression, trailing locomotor and grip strength deficits.Consistent with this, we found that phrenic MNs exhibit a molecular signature of MNs that are resilient to degeneration and show delayed cell death and axonal degeneration compared to limbMNs. We also found that phrenic and limb-innervating MNs receive largely different inputs, suggesting that ALS-associated changes to distinct motor circuits may differentially contribute to breathing and locomotor dysfunction. Phrenic MN distinct properties are largely dependent on transcriptional programs active during early development. **Therefore, we propose that an early phrenic MN-specific genetic program drives intrinsic and circuit-level properties that partially protect phrenic MNs from degeneration.**

Disclosures: R. Lopez de Boer: None. **P. Philippidou:** None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

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Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.02

Topic: C.06. Neuromuscular Diseases

Support: NIH 1RF1AG083085-01

Title: ALS selective vulnerability: corticospinal synapses preferentially contact and are engulfed by microglia, with substantially increased engulfment in hSOD1G93A mice

Authors: *J. FROBERG[1], J. KIM[2], H. LE[5], A. ENGMANN[6], M. A. VICENT[3], M. ROSS[4], J. D. MACKLIS[3];
[2]Pharmacol., [3]Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., [1]Harvard Univ., Cambridge, MA; [4]Dept. of Stem Cell and Regenerative Biol., Harvard Univ., Somerville, MA; [5]Stanford Med. Sch., San Jose, CA; [6]Dept. of Stem Cell and Regenerative Biol., Harvard University, Dept. of Stem Cell and Regenerative Biol., Cambridge, MA

Abstract: Mechanisms causing specific circuits to be selectively vulnerable in ALS are almost completely unknown; understanding them might illuminate ALS pathology and enable new therapeutics. ALS is principally degeneration of the cortico-spinal-neuromuscular junction circuit: both corticospinal neurons (CSN, "upper motor neurons") and spinal motor neurons ("lower motor neurons") specifically degenerate, while most related neuronal populations do not.

Using hSOD1G93A and WT mice, we report novel potential contributors to CSN circuit vulnerability in ALS: 1) preferential microglial contact with and engulfment of corticospinal synapses vs. unaffected glutamatergic synapses in WT, with 2) significantly increased engulfment of CSN synapses in hSOD1G93A mice.
To investigate molecular alterations in CSN axons and synapses in ALS, we developed approaches for fluorescent sorting of CSN-specific synaptosomes from thoracolumbar spinal cord (tlSC) and brainstem (co-BS) of hSOD1G93A mice at pre-onset and onset of motor system degeneration. This design exploits the spatial and temporal progression of SOD1-ALS pathology: motor deficits and motor neuron loss are earliest and most severe in tlSC, with much later brainstem involvement. We prioritized mRNAs both enriched in CSN synaptosomes vs. input and dysregulated in hSOD1G93A vs. WT. Strikingly, the majority fall into two functionally coherent categories: the C1q complement complex — the initiating step of complement-mediated synaptic pruning — and the disease-associated microglia (DAM) signature. This C1q/DAM dysregulation appears specifically in onset-stage tlSC synaptosomes, absent in pre-onset or co-BS synaptosomes.
We tested two non-exclusive models to elucidate this enrichment: (1) microglia might contact and engulf CSN synapses, inadvertently co-purifying microglial transcripts; or (2) CSN might intrinsically express and axonally traffic these transcripts for localized signaling. We find evidence for both: C1qa and Grn mRNA puncta localize within CSN axons, consistent with neuronal trafficking; but puncta are most abundant within microglia and frequently proximal to engulfed CSN material. CSN synapses contact microglia significantly more than other (ALS-unaffected) glutamatergic synapses, even in WT. We also find hSOD1G93A spinal microglia exhibit ~3-fold higher engulfment of CSN material vs. WT. Together, these findings support a model in which preferential corticospinal-microglial contacts at baseline, and substantially increased microglial engulfment of CSN synapses at onset of degeneration might contribute to selective CSN circuit vulnerability in ALS.

Disclosures: J. Froberg: None. **J. Kim:** None. **H. Le:** None. **A. Engmann:** None. **M.A. Vicent:** None. **M. Ross:** None. **J.D. Macklis:** None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.03

Topic: C.06. Neuromuscular Diseases

Support: NIH RF1NS127407 (BJW, CLT)
Cullen Young Investigator Award (AH)
Mussallem Transformative Scholars Award (AH)

Title: AP2A1 downregulation promotes multiple pathologies across neurodegenerative diseases

Authors: *R. KALIK[1], A. H. HELD[1], C. VIETS[1], G. ANEX[1], H. AHANGER[1], S. KEERTHIVASAN[1], I. FLESSAS[1], M. NAUMANN[3], S. POWLEY[1], M. YATES[1], S. LIM[1], C. MARQUES[1], A. HERMANN[3], M. W. ALBERS[1], K. WHITE[4], C. LAGIER-TOURENNE[1,5], B. J. WAINGER[1,5,2,6];
[1]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [2]Dept. of Anesthesiology, Critical Care and Pain Med., Massachusetts Gen. Hosp., Boston, MA; [3]Translational Neurodegeneration Section "Albrecht Kossel", Dept. of Neurol., Univ. Med. Ctr. Rostock, Univ. of Rostock, Rostock, Germany; [4]Cutaneous Biol. Res. Ctr., Massachusetts Gen. Hospital, Harvard Med. Sch., Charlestown, MA; [5]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA; [6]Harvard Stem Cell Inst., Cambridge, MA

Abstract: Pathological protein accumulations are a nearly universal feature of neurodegenerative diseases, and a better understanding of how these accumulations arise could enable therapeutic strategies promoting their clearance. We have found that AP2A1 is misregulated in Alzheimer's disease (AD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS), and that AP2A1 downregulation impairs the clearance of TDP-43, Aβ, and tau. AP2A1 is a subunit of the AP2 complex, which is primarily known for its role in clathrin-mediated endocytosis, but also binds the key autophagy regulator LC3. Using *Drosophila*, we find that AP2A1 knockdown increases neurodegeneration caused by TDP-43, Aβ, and tau. Furthermore, knockdown of other AP2 complex subunits causes a similar phenotype, suggesting that AP2A1 regulates TDP-43, Aβ, and tau through the AP2 complex. We then used CRISPRi to knock down AP2A1 and another AP2 subunit, AP2M1, in iPSC-neurons. Consistent with our results in *Drosophila*, knockdown of these subunits increased the accumulation of TDP-43, Aβ, and tau. To determine whether the AP2 complex regulates these pathological proteins through clathrin or LC3, we returned to our *Drosophila* models of TDP-43, Aβ, and tau. Knockdown of LC3 increased neurodegeneration in TDP-43 and tau flies, and clathrin knockdown had no effect. Surprisingly, neither LC3 nor clathrin knockdown increased neurodegeneration caused by Aβ, which suggests that another function of the AP2 complex may regulate Aβ. We then validated these results in iPSC-neurons, where we found that knocking down the LC3 processing enzyme ATG4B increased the accumulation of TDP-43 and tau, but not Aβ. To test whether the direct binding of AP2A1 to LC3 regulates TDP-43 and tau clearance, we mutated the LC3-interacting region (LIR) in AP2A1 (AP2A1[LIRmut]). Expression of AP2A1[LIRmut] in iPSC-neurons increased cytoplasmic TDP-43 and phosphorylated tau. Therefore, the direct binding of AP2A1 to LC3 is required for normal clearance of TDP-43 and phosphorylated tau. Finally, we used mouse models to validate key results across a third system. Cytoplasmic TDP-43 was increased in mice heterozygous for AP2A1 and in mice injected with an AAV expressing AP2A1[LIRmut] compared to mice injected with an AAV expressing AP2A1[WT]. These results support a model where reduced AP2A1 function across three neurodegenerative diseases promotes multiple pathologies. Restoring AP2A1-mediated proteostasis may therefore be an attractive therapeutic strategy capable of mitigating pathological accumulations in several neurodegenerative diseases.

Disclosures: R. Kalik: None. **A.H. Held:** None. **C. Viets:** None. **G. Anex:** None. **H. Ahanger:** None. **S. Keerthivasan:** None. **I. Flessas:** None. **M. Naumann:** None. **S. Powley:** None. **M. Yates:** None. **S. Lim:** None. **C. Marques:** None. **A. Hermann:** None. **M.W. Albers:** None. **K. White:** None. **C. Lagier-Tourenne:** None. **B.J. Wainger:** None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

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Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.04

Topic: C.06. Neuromuscular Diseases

Support: Healey & AMG Center for ALS Young Investigator Award (Byrne Family and Judith & Pape Adams Fellow) Research Fellowship
Charities Aid Foundation (Wood Family)

Title: ALS-associated FAM69A-EVI5 fusion transcript is detectable in human ALS tissue and impairs cellular viability

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by widespread disruption of RNA metabolism, including altered splicing and intron retention. We recently identified 156 recurrent ALS-associated fusion transcripts using short-read RNA-sequencing data from the New York Genome Center (NYGC) ALS consortium (443 ALS individuals and 114 controls). Notably, whole genome sequencing data did not support the presence of these fusion events at the genomic level, suggesting that they may arise from aberrant RNA processing rather than DNA rearrangement. While fusion transcripts are well established in cancer, their contribution to neurodegenerative diseases remains poorly understood.

To validate ALS-associated fusion transcripts in an independent cohort, we performed long-read PacBio Iso-Seq on cerebellar tissue from Massachusetts General Hospital, comprising 48 ALS and 18 control individuals. This analysis confirmed 44.6% of ALS-specific fusion junctions previously identified in the NYGC cohort. Among the long-read confirmed candidates, *FAM69A-EVI5* emerged as a top fusion transcript of interest as it is predicted to preserve an open reading frame and joins sequences from *FAM69A*, a predicted endoplasmic reticulum-associated kinase, to *EVI5*, a regulator of Rab11 activity and a gene previously associated to Multiple Sclerosis.

We next developed a junction-specific BaseScope assay -a sensitive RNA *in situ* hybridization technique- and confirmed the presence of *FAM69A-EVI5* in ALS cerebellar tissue. To assess the functional consequences of this fusion transcript, SH-SY5Y cells expressing FAM69A-EVI5, the corresponding parental constructs or mCherry were analyzed using longitudinal readouts such as live-cell imaging, CYQUANT NF assay, and propidium iodide flow cytometry. Across these complementary experiments, FAM69A-EVI5 expression was associated with impaired cellular viability compared to mCherry control.

Together, these findings identify *FAM69A-EVI5* as an ALS-associated fusion transcript that is detectable in human disease tissue and can perturb cellular viability *in vitro*. Overall, this work

supports the concept that non-canonical RNA products generated by disrupted RNA processing may represent reproducible and functionally relevant features of ALS pathobiology.

Disclosures: A. Boudi: None. **H. Xu:** None. **T. Petrozziello:** None. **E. Granucci:** None. **J. Lemanski:** None. **B. Jana:** None. **K. Ghosh:** None. **P. Hornbostel:** None. **M. Kesavan:** None. **A. Castillo-Torres:** None. **R.B. Monsanto:** None. **C. de Esch:** None. **J. Berry:** None. **M. Cudkowicz:** None. **R. Mouro Pinto:** None. **D. Gao:** None. **G. Sadri-Vakili:** None.

Nanosymposium

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Location: WCC Rm 146C

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Presentation Number: NANO47.05

Topic: C.06. Neuromuscular Diseases

Support: NIH T32 GM145470

Title: Retrotransposon-derived proteins redirect UBQLN2 protein quality control during cellular stress

Authors: *N. GROTEWOLD[1], L. M. SHARKEY[2];
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Abstract: Endogenous retrovirus-like proteins expressed in the human nervous system likely contribute to neurodegenerative disease processes. One neurodegenerative disease protein known to interact with retrovirus-like proteins is UBQLN2, a ubiquitin-proteasome shuttle factor implicated in amyotrophic lateral sclerosis, frontotemporal dementia, and Huntington's disease (HD). UBQLN2 recognizes ubiquitin-tagged substrates in the cytoplasm, delivering them to the proteasome for degradation. In HD models, however, UBQLN2 also enters neuronal nuclei where it facilitates mutant huntingtin clearance. Our prior work showed that the retrovirus-like protein RTL8 promotes UBQLN2 movement to subnuclear compartments, and together with a second retrovirus-like protein, PEG10, recruits UBQLN2 under stress conditions to stress granules. These findings suggest retrovirus-like proteins regulate both the subcellular localization and client-recognition behavior of UBQLN2. UBQLN2, in turn, regulates levels of both RTL8 and PEG10, the latter of which we've found is a stress-induced protein.
Here we sought to determine how UBQLN2 regulates PEG10 under basal and stress conditions. We find that cellular stress increases PEG10 in immortalized cells, neurons, and brain-like organoids at the post-transcriptional level. Unlike the canonical UBQLN2 substrate TRIM32, which requires ubiquitination to be recognized and cleared by UQBLN2, PEG10 continues to bind to UQBLN2 and be degraded even in the absence of ubiquitination. An engineered UBQLN2 mutant (L619A) that cannot bind ubiquitin still interacts with PEG10, further supporting ubiquitin-independent regulation of PEG10 by UBQLN2 under basal conditions. Moreover, under basal conditions RTL8 is required for UBQLN2-PEG10 interaction, but during heat shock or oxidative stress this interaction occurs independent of RTL8. Collectively, our

results suggest UBQLN2-dependent PEG10 clearance limits PEG10 accumulation and tunes stress-responsive protein quality control. This work positions the endogenous retrovirus-like proteins RTL8 and PEG10 as regulators of the interface between cellular stress, subcellular proteostasis, and neurodegenerative disease mechanisms.

Disclosures: N. Grotewold: None. **L.M. Sharkey:** None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

Location: WCC Rm 146C

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Presentation Number: NANO47.06

Topic: C.06. Neuromuscular Diseases

Title: Tissue-specific causal modeling using Gemini Digital Twins links C9orf72 repeat expansion to spinal cord microglial programs and ALS progression

Authors: *L. SUN, W. ZHU, S.-Y. SHIN, J.-M. GRIES, J. LATOURELLE;
AITIA, Cambridge, MA

Abstract: Objective: C9orf72 repeat expansion (C9 RE) is the most common genetic cause of amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), but the molecular mechanisms by which it contributes to ALS progression remain incompletely understood. We aimed to investigate the pathogenic mechanism of C9 RE in ALS progression across multiple post-mortem central nervous system tissues.Methods: Using AITIA's proprietary REFS™ causal AI platform, we built tissue-specific ALS Gemini Digital Twins (GDT) from Target ALS Postmortem Tissue Core data, incorporating C9 RE, RNA sequencing, survival outcomes and other clinical and molecular covariates. GDTs were generated separately for cervical (N=156) and lumbar (N=146) spinal cord and cerebellum (N=164). Causal relationships were estimated using counterfactual perturbation analysis, enabling identification of genes that mediate the effect of C9 RE on clinical outcomes. Tissue-specific cell proportions were estimated using RNA deconvolution.Results: Across all GDTs, C9 RE decreased C9orf72 RNA expression and shortened overall survival. However, C9orf72 RNA expression itself was not causally linked to survival, suggesting that expansion-associated disease progression may not be primarily mediated by reduced transcript abundance. Instead, several mediator genes were identified whose RNA expression was driven by C9 RE and causally linked to survival. These genes were primarily observed in the spinal cord GDTs and were enriched for innate immune, endocytic, and reactive oxygen species-related programs. Cervical mediator genes showed strong enrichment in microglial pathogen phagocytosis and the TYROBP microglial causal network. Notably, the microglial/macrophage-secreted genes GPNMB and CHIT1 were consistently identified as key mediators linking C9 RE and survival in both spinal cord GDTs. Consistent with these findings, RNA deconvolution analysis indicated higher estimated microglial cell proportion in C9 RE carriers than in non-carriers in spinal cords. Conclusions: These findings suggest that C9 RE contributes to ALS progression through tissue-specific molecular and cellular mechanisms

beyond reduced C9orf72 RNA expression. Survival-relevant effects were most prominent in spinal cords and converged on glial remodeling, microglial activation, and inflammatory mediators. GPNMB and CHIT1, nominated consistently by both spinal cord GDTs, may reflect distinct microglia/macrophage activation states. Together, these results suggest that spinal cord microglial pathways, including GPNMB- and CHIT1-associated programs, may mediate C9orf72-linked ALS progression.

Disclosures: L. Sun: A. Employment/Salary (full or part-time):; AITIA. **W. Zhu:** None. **S. Shin:** A. Employment/Salary (full or part-time):; AITIA. **J. Gries:** A. Employment/Salary (full or part-time):; AITIA. **J. Latourelle:** A. Employment/Salary (full or part-time):; AITIA.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.07

Topic: C.06. Neuromuscular Diseases

Title: Circulating Extracellular Vesicle Lipid Alterations Define Systemic Biomarkers of Disease Biology in ALS and Enable Monitoring of Therapies Targeting Underlying Mechanisms

Authors: *V. RICOTTI[1], A. FOGEL[1,2,4], F. CERRI[5], R. ROSSI[1], P. ALA[1], A. CAPSTICK[3], F. GERARDI[5], R. JACOBS[6], E. MERCURI[7], V. SANSONE[5], P. SHAW[8], M. VANDENBOSCH[6], T. HENDRIKS[6], C. WALSH[9], R. NILFOROOSHAN[9], P. BARNAGHI[2,4], **T. VOIT**[1,10]; [1]Vesalic Limited, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom; [3]Imperial Col. London, Ashford, United Kingdom; [4]Care Res. and Technol. Centre, UK Dementia Res. Inst., London, United Kingdom; [5]Univ. degli Studi di Milano and Ctr. Clinico NeMO, Milano, Italy; [6]Maastricht Univ., Maastricht, Netherlands; [7]Catholic Univ. of the Sacred Heart, rome, Italy; [8]Sheffield Inst. for Translational Neurosci. (SITraN), Univ. of Sheffield, Sheffield, United Kingdom; [9]Surrey and Borders Partnership NHS Fndn. Trust (SABP), Surrey, United Kingdom; [10]NIHR Great Ormond Street Hosp. Biomed. Res. Centre, Univ. Col. London, London, United Kingdom

Abstract: Background: Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative disorder with no biomarkers capturing underlying disease biology or enabling early detection. Despite emerging evidence implicating systemic alterations in pathophysiology, robust circulating signatures supporting stratification or monitoring remain lacking.**Methods:** Extracellular vesicles (EVs) were isolated from serum of ALS patients (n=77), individuals with motor neuron disease subforms (primary lateral sclerosis, progressive muscular atrophy), spinal muscular atrophy (SMA) patients (n=50), and neurologically healthy controls (n=81). High-dimensional mass spectrometry-based lipidomic profiling was performed. A machine learning framework analysis was applied for classification and model interpretation. Continuous disease probability outputs were derived from multivariate modelling. Longitudinal profiles were evaluated in superoxide dismutase 1 (SOD1)-ALS patients receiving Tofersen, and

generalisability assessed in an independent external cohort. The analytical approach was initially developed and optimised in ALS and subsequently applied across independent Parkinson's disease (PD) and Alzheimer's disease (AD) cohorts to evaluate cross-disease applicability.
Results: ALS was characterised by a distinct multi-feature circulating EV lipidomic fingerprint reflecting coordinated membrane remodelling, enabling accurate discrimination from healthy controls and related neuromuscular diseases (area under the receiver operating characteristic curve [AUROC] 0.93, 95% CI 0.88-0.99). The signature was preserved across sporadic and monogenic ALS, indicating convergence onto shared disease biology. Continuous probabilistic outputs supported stratification beyond binary classification. Longitudinal analysis in Tofersen-treated SOD1-ALS patients showed dynamic modulation of EV lipidomic trajectories parallel to clinical measures. SMA exhibited a distinct lipid fingerprint, supporting disease specificity. When applied to PD and AD, a trained model (with a smaller set of samples) revealed disease-specific yet biologically structured lipid patterns, preliminary evidence of shared systemic lipid dysregulation rather than disease-agnostic classification.
Conclusions: EV lipidomic signatures define a systemic blood-based biomarker platform reflecting core pathogenic processes in ALS, supporting diagnosis, stratification, and therapeutic monitoring. Preliminary evidence of analogous signatures in AD and PD suggests a shared framework of systemic lipid dysregulation across neurodegeneration.

Disclosures: V. Ricotti: A. Employment/Salary (full or part-time):; Co-founder & CEO of Vesalic. **A. Fogel:** A. Employment/Salary (full or part-time):; Employee and optionholder, Vesalic Ltd. **F. Cerri:** Other; Consultant and optionholder, Vesalic Ltd. **R. Rossi:** A. Employment/Salary (full or part-time):; Employee and shareholder, Vesalic Ltd. **P. Ala:** A. Employment/Salary (full or part-time):; Employee and optionholder, Vesalic Ltd. **A. Capstick:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd.. **F. Gerardi:** None. **R. Jacobs:** None. **E. mercuri:** None. **V. Sansone:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **P. Shaw:** F. Consulting Fees (e.g., advisory boards); Consultant, Vesalic Ltd. **M. Vandenbosch:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **T. Hendriks:** Other; Consultant and optionholder, Vesalic Ltd. **C. Walsh:** None. **R. Nilforooshan:** Other; Consultant and optionholder, Vesalic Ltd. **P. Barnaghi:** F. Consulting Fees (e.g., advisory boards); Consultant and optionholder, Vesalic Ltd. **T. Voit:** Other; Co-founder and shareholder, Vesalic Ltd..

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R00NS118109

Title: Graphical neural networks uncover cell-type-resolved mechanisms invisible to differential expression analysis and nominate druggable targets in amyotrophic lateral sclerosis

Authors: *H. XU[1,3,4], Y. LIU[1,4], A. BOUDI[3,2,5], T. PETROZZIELLO[3,2,6], G. SADRI-VAKILI[3,2,5], D. GAO[1,3,4];
[1]Ctr. for Genomic Med., [2]Sean M. Healey & AMG Ctr. for ALS at Mass Gen., Massachusetts Gen. Hosp., Boston, MA; [3]Dept. of Neurol., Mass Gen. Brigham and Harvard Med. Sch., Boston, MA; [4]Program in Med. and Population Genet., Broad Inst. of Harvard and MIT, Cambridge, MA; [5]Mass Gen. Brigham Neurosci. Inst., Mass Gen. Brigham, Boston, MA; [6]Lurie Ctr. for Autism, Dept. of Pediatrics, Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is fatal within 2-5 years, with no treatment halting progression. This therapeutic void persists because the field lacks druggable targets rooted in ALS's mechanistic complexity: heritable mutations explain only ~10-15% of cases, leaving most patients without an actionable gene. The transcriptome captures convergent genetic and environmental effects, yet RNA-seq has failed to deliver curative targets because differentially expressed gene (DEG) analysis treats genes as independent additive variables that miss network-level disruptions. To model these non-additive interactions, we built a graph neural network (GNN) over an assembled knowledge graph including Gene Ontology, where each pathway node nonlinearly integrates member-gene expression and propagates downstream to classify ALS vs. control. By weighting synergies among small-effect genes, the model reveals disease patterns invisible to DEG analysis.We integrated bulk RNA-seq from postmortem cortex and spinal cord (NYGC and GTEx; 460 ALS, 439 controls), followed by tissue-matched and single-cell-guided (~52,000 cells) deconvolution into six neuronal and glial cell types. The trained GNN distinguished ALS from control with F1 = 0.990 on held-out data and 0.973 on an independent MGH cohort, outperforming two published bulk-expression models by >10% in accuracy. Importantly, it also distinguished ALS from control in iPSC-derived motor neurons (iMNs), suggesting it learns generalized signatures unbiased by postmortem status.The model highlighted 221 genes significantly contributing to ALS across cell types. About 65% were non-DEGs with only moderate fold changes, yet synergistically disrupted apoptosis, transmembrane signaling, and neuroinflammation pathways. Top-10 contributors included *ROCK1*, a non-DEG significantly predicting ALS in excitatory neurons and astrocytes; its inhibitor fasudil recently completed a phase 2 trial for ALS.We thus hypothesize that drugs reducing the GNN's predicted ALS probability will ameliorate disease phenotypes, enabling in silico drug repurposing. As proof-of-concept, we tested riluzole, an FDA-approved ALS drug, by mapping its iMN-derived expression changes onto patient motor neurons. ALS probability dropped significantly ($p < 2.2e-16$), and rescued pathways matched riluzole's known mechanisms. We present a novel framework that unravels overlooked transcriptional signals in complex disorders and pinpoints therapeutic opportunities.

Disclosures: H. Xu: None. **Y. Liu:** None. **A. Boudi:** None. **T. Petrozziello:** None. **G. Sadri-Vakili:** None. **D. Gao:** None.

Nanosymposium

NANO47: ALS and Motor Neuron Diseases: Human Genetics and Cellular Mechanisms

Location: WCC Rm 146C

Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.09

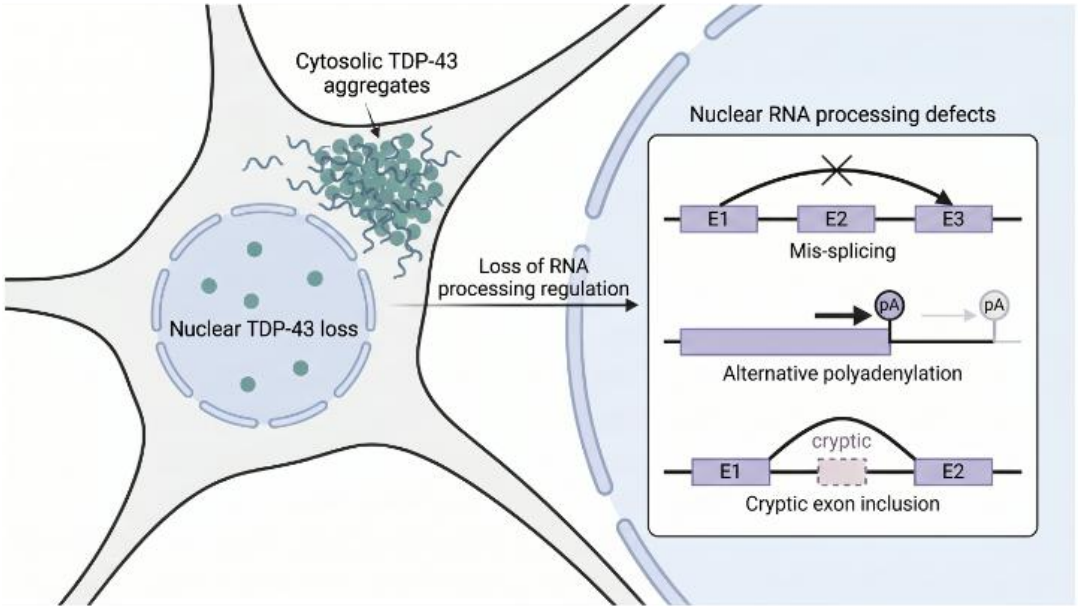
Topic: C.06. Neuromuscular Diseases

Support: NIH R35 NS122140

Title: TDP-43 dysregulation of polyA site selection in age-related neurodegeneration

Authors: *C. M. STOCKFORD[1], A. LA SPADA[2];
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Abstract: Many neurodegenerative disorders have unknown etiologies, but share the common pathological feature of nuclear clearance and cytoplasmic aggregation of TAR DNA-binding protein 43 (TDP-43). TDP-43, an RNA-binding protein that directly binds over 6,000 RNAs, plays a key role in the pathogenesis of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Recently, TDP-43 dysregulation of RNA splicing emerged as a fundamental event in these diseases; however, TDP-43 can also regulate polyadenylation (Figure), the length of RNA distinct 3′ untranslated regions (3′ UTRs), a process that had not been studied.
Here, we applied the dynamic analysis of polyadenylation from an RNA-Seq (DaPars) tool to ALS/FTD transcriptome datasets and report extensive alternative polyadenylation (APA) upon TDP-43 alteration in ALS/FTD cell models and postmortem ALS/FTD neuronal nuclei. To determine the functional relevance of APA elicited by TDP-43 depletion, we studied APA of microtubule affinity regulating kinase 3 (MARK3) in human neuroblastoma cells, induced pluripotent stem cell (iPSC)-derived motor and cortical neurons, as well as postmortem ALS/FTD tissue.
Loss of TDP-43 increased expression of *MARK3* transcripts with longer 3′ UTRs, corresponding with a change in the subcellular distribution of MARK3 protein, which increased its localization in neurites relative to soma. MARK3 is a tau kinase linked to tau hyperphosphorylation in Alzheimer's disease, so we examined tau phosphorylation in TDP-43-depleted iPSC-derived neurons. We found increased tau phosphorylation, which was reduced to wildtype levels by a MARK3 inhibitor.
Altogether, our findings define broad changes in APA and highlight an important mechanistic link between TDP-43 dysfunction and tau regulation. Thus, APA events in TDP-43 proteinopathies could be targets for therapeutic intervention to reduce dysfunction of RNA transcripts, thereby rescuing disease phenotypes.



Disclosures: C.M. Stockford: None. **A. La spada:** None.

Nanosymposium

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Presentation Number: NANO47.10

Topic: C.06. Neuromuscular Diseases

Support: NINDS Intramural Funding

Title: Pathological R-loop Depletion disrupts Astrocytic Stress Biology in ALS4

Authors: *J. VIRGA[1], C. GRUNSEICH[2];
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Abstract: Amyotrophic lateral sclerosis type 4 (ALS4) is a rare, juvenile-onset, autosomal dominant motor neuron disease caused by gain-of-function mutations in Senataxin (*SETX)*, a DNA/RNA helicase that regulates transcription-associated R-loops. Defining how *SETX* mutations alter RNA and transcriptional biology is a critical unmet need in ALS4. While abnormal R-loop accumulation has been implicated in neurodegeneration, far less is known about whether pathological R-loop depletion can also disrupt cellular stress responses and RNA processing. We observe increased astrogliosis in ALS4 patient spinal cord tissue and hypothesize

that *SETX* gain-of-function drives astrocytic dysfunction by depleting R-loops, disruption of stress-responsive RNA biology, and non-cell autonomous injury to motor neurons. Here, we show that ALS4 lumbar spinal cord (n = 3/group) exhibits reduced R-loop signal (p = <0.0001), increased astrocytic reactivity (p = 0.016), and abnormal TDP-43 localization in both motor neurons and non-neuronal cells. We also detected *STMN2* cryptic exon inclusion in ALS4 tissue, linking these changes to a disease-relevant RNA missplicing event. In an isogenic iPSC-derived astrocyte model, ALS4 cells similarly display reduced nucleolar R-loops (p = 0.029) and a reactive phenotype at baseline. To assess how the *SETX* mutation affects stress responses, we performed acute heat shock experiments. Following heat shock, we observe that ALS4 astrocytes (n = 4/group) show a blunted stress response, including impaired recruitment of stress granule (SG) proteins (p = 0.0002), formation of fewer stress granules (p = 0.009), and accelerated granule disassembly (p = <0.0001). During recovery, wild-type astrocytes form nuclear TDP-43 condensates that colocalize with phospho-TDP-43 (p = 0.001), whereas ALS4 astrocytes retain diffuse nuclear TDP-43 and form fewer condensates (p = 0.002), consistent with impaired stress-induced TDP-43 reorganization. ALS4 astrocytes also show greater persistence of HSP70, a prominent TDP43 chaperone, in the nucleolus after stress (p = 0.013), suggesting engagement of an altered proteostatic recovery pathway. We propose that *SETX* gain-of-function depletes stress-responsive R-loops that normally help coordinate stress granule assembly, leading to the inability to mount an appropriate stress response. These findings identify pathological R-loop depletion in ALS4 astrocytes and support a model in which *SETX* gain-of-function disrupts astrocytic stress RNA biology, TDP-43 localization, and RNA splicing. This work provides a new framework for how astrocyte RNA dysfunction may contribute to ALS4 pathogenesis.

Disclosures: J. Virga: None. **C. Grunseich:** None.

Nanosymposium

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Topic: C.06. Neuromuscular Diseases

Support: KDA WG Fellowship Award
R01-NS121374
IGNITE R61-NS133212

Title: Skeletal Muscle Cell Fate Determines Neuromuscular Junction Integrity in SBMA

Authors: *C. RODRIGUES[1], B. DE FREITAS BRENHA[2], H. C. MIRANDA[1];
[1]Dept. of Genet. and Genome Sci., [2]Case Western Reserve Univ., Cleveland, OH

Abstract: Spinal and bulbar muscular atrophy (SBMA) is a disorder caused by a CAG repeat expansion mutation in the androgen receptor (AR) gene. While classically considered a motor neuron disease, accumulating evidence implicates skeletal muscle as a primary driver of disease

onset and progression, yet the mechanistic basis of muscle-intrinsic dysfunction in human tissue remains undefined. To systematically interrogate how AR CAG repeat length influences SBMA pathogenesis, we generated a first-of-its-kind panel of isogenic human iPSC lines with 5, 26, 37, 50, and 62 CAG repeats using CRISPR/Cas9 gene editing technology. This isogenic panel allows us to determine whether transcriptional and functional phenotypes scale linearly with repeat length or emerge beyond a pathological threshold, a question no prior human study has systematically addressed. To model the human neuromuscular junction (NMJ), we co-cultured iPSC-derived motor neurons with skeletal muscle, achieving robust NMJ formation within 10 days. SBMA (50Q) co-cultures exhibited reduced NMJ number and size and impaired NMJ function measured on a multi-well multi-electrode array (MEA) system. Critically, mix-and-match experiments revealed that SBMA motor neurons did not impair isogenic control skeletal muscle, whereas SBMA skeletal muscle alone was sufficient to drive NMJ dysfunction, positioning muscle as the primary pathological driver. To define the transcriptional basis of this muscle-intrinsic dysfunction, we performed scRNA-seq on SBMA (50Q) and isogenic control (26Q) NMJ co-cultures with and without the AR ligand, dihydrotestosterone (DHT), stimulation. We identified major cell populations including fast and slow-twitch skeletal muscle subtypes, motor neurons, and undifferentiated progenitors. SBMA co-cultures exhibited a pronounced shift in muscle fiber-type composition and expansion of undifferentiated populations, indicating impaired maturation and altered cell fate dynamics. Together, these findings establish that polyQ-expanded AR drives a pathological reprogramming of skeletal muscle cell fate that is sufficient to destabilize the NMJ and impair neuromuscular function in SBMA. Ongoing work using our full isogenic CAG repeat series is defining the repeat-length threshold at which these phenotypes emerge and testing whether restoring fiber-type composition rescues NMJ integrity, nominating muscle fiber-type reprogramming as a tractable and novel therapeutic axis in SBMA.

Disclosures: C. Rodrigues: None. **B. de Freitas Brenha:** None. **H.C. Miranda:** None.

Nanosymposium

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Time: Wednesday, November 18, 2026, 1:00 PM - 4:00 PM

Presentation Number: NANO47.12

Topic: C.06. Neuromuscular Diseases

Title: Post Transcriptional regulation in the landscape of aging and nerve injury

Authors: *A. RAMNATH[1], F. ARNOLD[2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease (MND) characterized by progressive neurodegeneration and TDP-43 pathology. While transcriptional dysregulation is characteristic of ALS, the post-transcriptional mechanisms that amplify and cause neuronal dysfunction remain poorly understood. We recently studied the role of alternative polyadenylation (APA) as a crucial post-transcriptional mechanism linking TDP-43 dysfunction

to MND pathogenesis in neuronal cell models and in ALS postmortem tissue. We found that APA dysregulation drives altered 3′ UTR landscapes and aberrant isoform expression in human neurons. These APA-driven changes impact mRNA stability and subcellular localization of disease-relevant transcripts, underscoring the functional relevance of TDP-43-mediated APA.Building on this work, we are now disentangling post-transcriptional regulation observed in the context of TDP-43 depletion from the changes that are observed in the context of aging and nerve injury. Our preliminary data suggest that APA dysregulation is not only a downstream consequence of TDP-43 pathology, but also a coordinated mechanism by which human neurons respond to injury and normal aging. Using a mouse model of sciatic nerve crush we observed a striking shift towards proximal polyadenylation sites (PASs) (70%) shortly after injury followed by a shift towards distal PASs (77%) during the recovery phase. In a parallel study, we found a global shift towards distal PASs in transdifferentiated (‘aged’) neurons relative to induced pluripotent stem cell (iPSC)-derived (‘young’) neurons from the same donor fibroblasts, with significant enrichment of RNA binding proteins among the affected genes.These findings position APA as not only a novel layer of post-transcriptional regulation in ALS, but as a key mechanism by which neurons regulate gene expression in response to injury and aging.

Disclosures: A. Ramnath: None. **F. Arnold:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.01

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

Support: NIH Grant AG062509
NIH Grant AG041274
NIH Grant AG070761

Title: Zinc Finger Protein 580 Contributes to the Pathogenesis of Postoperative Delirium by Mediating the Bone Marrow-Brain Axis in Aged Mice

Authors: *S. FU[1], W. ZHANG[2], Y. ZHANG[3], Z. XIE[2];
[2]Anesthesiol., [1]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA

Abstract: Introduction: Postoperative delirium (POD) is associated with increased morbidity, mortality, and long-term risk of Alzheimer’s disease; however, its underlying mechanisms remain poorly understood. Emerging evidence suggests a bidirectional communication between the bone marrow and the brain. Zinc Finger Protein 580 (Znf580), a C2H2-type zinc finger protein, exhibits both neuroprotective properties and regulatory roles in hematopoiesis. Our preliminary data revealed a marked decrease in plasma Znf580 levels following anesthesia/surgery (A/S) in aged mice, mirroring a decline in the cortex but contrasting with

significant upregulation in the bone marrow. This study investigates whether Znf580 contributes to POD-like behavior via the bone marrow-brain axis and evaluates its potential as a therapeutic target.
Methods: Eighteen-month-old female C57BL/6J mice underwent exploratory laparotomy under 1.4% isoflurane and 40% oxygen. ZNF580 levels in plasma, cortex, and bone marrow were quantified via ELISA, immunofluorescence, and Western blotting. Bone marrow immune cell populations were identified via flow cytometry, and scRNA-seq was conducted to profile key cell populations and molecular pathways.
Results: A/S reduced Znf580 protein levels in plasma and cortex, but increased levels in the bone marrow, with no significant changes in other organs. This bone marrow upregulation was attributed to the retention of $Znf580^{+}$ macrophages. Pseudobulk analysis of scRNA-seq data indicated that bone marrow Znf580 upregulation coincided with enhanced protein synthesis and altered leukocyte retention, validated by changes in key proteins (e.g., Vcam1, Cxcl12). Single-cell profiling revealed that Znf580 was specifically upregulated in macrophages. Functional enrichment analysis showed that these $Znf580^{+}$ macrophages transition from a baseline proliferative state to a highly active regulatory state post-A/S. CellChat analysis demonstrated a significant increase in the number and strength of interactions involving $Znf580^{+}$ macrophages, identifying them as a central communication hub following A/S, characterized by disease-specific signaling and the amplification of existing pathways.
Conclusion: These findings suggest that A/S induces the retention of $Znf580^{+}$ macrophages in the bone marrow, disrupting the bone marrow-brain axis and impairing Znf580 delivery to the brain. By acting as a central signaling hub, these macrophages orchestrate bone marrow crosstalk and systemic inflammation. This study identifies Znf580 as a critical therapeutic target for the prevention and treatment of POD in the elderly.

Disclosures: S. Fu: None. **W. Zhang:** None. **Y. Zhang:** None. **Z. Xie:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.02

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

Support: NIH R21 AG065606-01A1
NIH R01 AG070257-01
NIH R21 5R21AG081763
MGH Sundry Fund

Title: Transmission of Alzheimer's disease-associated microbiota dysbiosis in Tau P301S mice

Authors: W. QI[1], **C. HUANG**[1], Z. XIE[2], *Y. ZHANG[3];
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[2]Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hosp. and Harvard Med. Sch., Houston, TX; [3]Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA

Abstract: Introduction: Clinical studies have shown that partners of Alzheimer's disease (AD) patients are at an increased risk of developing dementia, likely due to shared environmental factors that influence the gut microbiota (GMB) [1]. Our previous clinical studies indicated that the GMB profiles of partners of AD patients closely resemble those of AD patients but differ significantly from those of non-AD controls. In parallel, our previous mouse studies showed that wild-type (WT) mice co-housed with 5xFAD mice developed AD-associated GMB dysbiosis and exhibited cognitive impairments [2]. To investigate whether GMB dysbiosis can also be transmitted in other AD mouse models, we extended our studies to Tau P301S transgenic mice [3] using the same co-housing paradigm. **Methods:** Three-month-old male WT mice were co-housed with age- and sex-matched Tau P301S transgenic mice for up to 3 months. The co-housed WT mice are referred to as AD-exposed WT (ADWT) mice (Fig. 1a). Fecal samples were collected at 6 months of age, and gut microbiota profiles were analyzed using shotgun metagenomic sequencing. **Results:** PCoA analysis showed that the GMB profile of AD-exposed WT (ADWT) mice closely resembled that of Tau P301S mice but differed from WT mice. Species-level analysis revealed GMB dysbiosis, particularly within the Lachnospiraceae family, and functional analysis indicated distinct GMB functions among the three groups. **Conclusion:** Our study demonstrates that WT mice co-housed with Tau P301S transgenic mice acquired AD-associated GMB dysbiosis, suggesting that GMB dysbiosis may be transmissible and could contribute to AD-related pathophysiology through impaired SCFA-mediated gut-brain axis regulation. References: [1] de Vugt, M. et al. Age Ageing 35, 160-166 (2006). [2] Zhang, Y. et al. Mol Psychiatry 28, 4421-4437 (2023). [3] Holtzman, D. et al. Alzheimer Dement 12, 1033-1039 (2016).

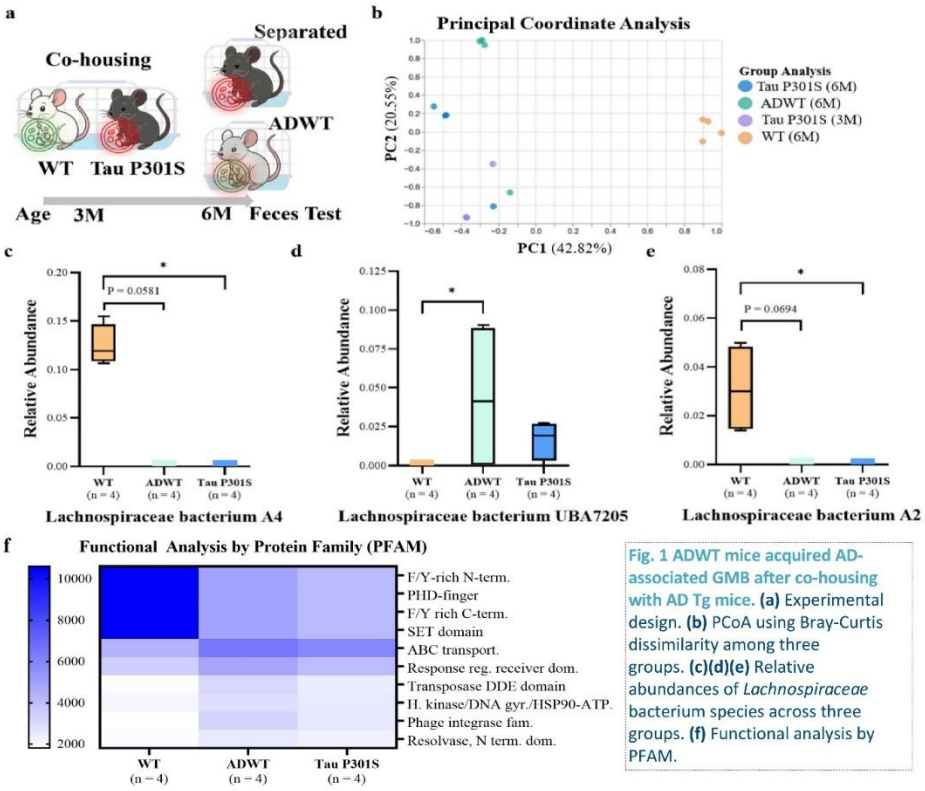


Fig. 1 ADWT mice acquired AD-associated GMB after co-housing with AD Tg mice. **(a)** Experimental design. **(b)** PCoA using Bray-Curtis dissimilarity among three groups. **(c)(d)(e)** Relative abundances of *Lachnospiraceae* bacterium species across three groups. **(f)** Functional analysis by PFAM.

Disclosures: W. Qi: None. **C. Huang:** None. **Z. Xie:** None. **Y. Zhang:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.03

Topic:

Title: Longitudinal Gut Microbiota and Metabolomic Signatures Associated with Postpartum Depressive Symptoms: Preliminary Findings from a Prospective Cohort Study

Authors: S. YANG[1], M. WANG[4], Y. HE[2], Y. ZHANG[5], S. SHEN[2], *J. WANG[3];
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[3]Massachusetts Gen. Hosp., andover, MA; [4]The First hospital of Jilin Univ., Changchun, China;
[5]Anesthesia, Critical Care and Pain Med., Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA

Abstract: Postpartum depression affects approximately 10-15% of women and is associated with adverse maternal and infant outcomes. Emerging evidence suggests that gut microbiota-associated immune and metabolic processes may be linked to mood regulation; however, prospective multi-omic studies in postpartum populations remain limited. This prospective pilot cohort study examined gut microbiome composition and circulating metabolomic profiles associated with postpartum depressive symptoms. Maternal rectal swab and blood samples were collected prior to delivery. Shotgun metagenomic sequencing was used to characterize microbial composition, and metabolomic profiling was performed using LC-MS/MS. Participants were stratified into postpartum depressive symptom (Dep, n = 4) and non-depressive symptom (Non-Dep, n = 26) groups based on postpartum Edinburgh Postnatal Depression Scale (EPDS) scores. Species-level microbiome analyses did not identify statistically significant differences in relative abundance between groups after multiple-comparison correction. However, exploratory analyses suggested differences in microbial community composition between groups. Gardnerella vaginalis was detected in all participants who subsequently developed postpartum depressive symptoms and in a subset of controls. Given the limited sample size, this observation should be considered exploratory and requires validation in larger cohorts. Metabolomic analyses identified significantly lower late-pregnancy concentrations of 3-hydroxybutyric acid and acetoacetic acid among women who subsequently developed postpartum depressive symptoms following Benjamini-Hochberg false discovery rate correction, suggest potential alterations in ketone body metabolism prior to symptom emergence. These preliminary findings suggest that microbiota-associated metabolic alterations, particularly involving ketone body metabolism, may be associated with the emergence of postpartum depressive symptoms and warrant validation in larger prospective studies.

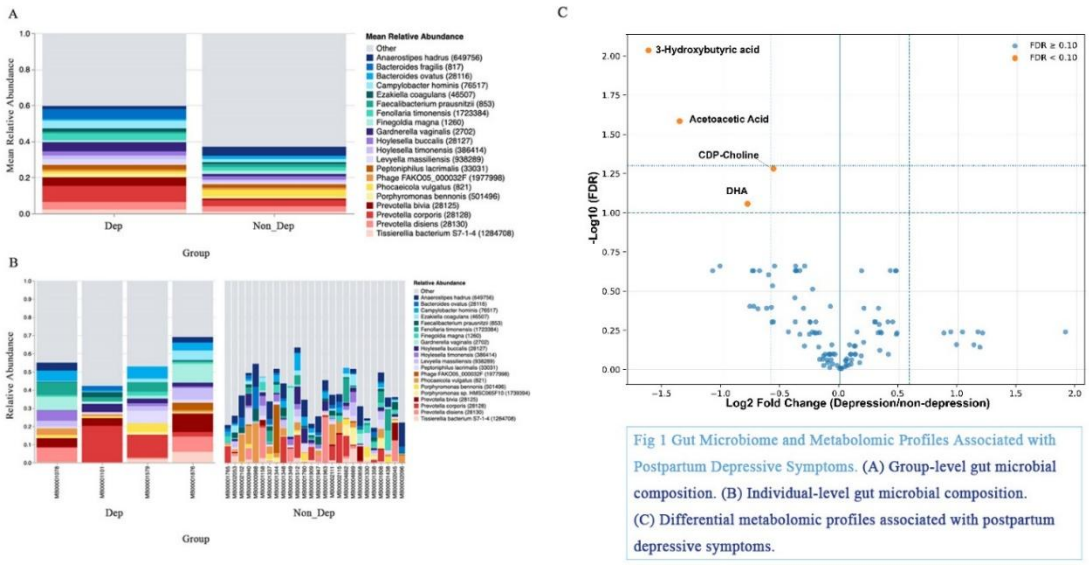


Fig 1 Gut Microbiome and Metabolomic Profiles Associated with Postpartum Depressive Symptoms. (A) Group-level gut microbial composition. (B) Individual-level gut microbial composition. (C) Differential metabolomic profiles associated with postpartum depressive symptoms.

Disclosures: S. Yang: None. **M. Wang:** None. **Y. He:** None. **Y. Zhang:** None. **S. Shen:** None. **J. Wang:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.04

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

Support: NIH Grant R01 AG07669

Title: Mild magnetothermal stimulation disrupts Aβ plaques and renders them susceptible to microglia-mediated clearance

Authors: *M. NAVEED, M. PULEO, M.-H. KIM;
Dept. of Biol. Sci., Kent State Univ., Kent, OH

Abstract: The aggregation of amyloid-beta (Aβ) from monomers into intermediate oligomers and ultimately fibrils and plaques is a pathological hallmark of Alzheimer's Disease (AD). Among these forms of Aβ, the oligomers are recognized as the primary drivers of AD pathogenesis. As such, mechanical or pharmacological disaggregation of Aβ plaques can exacerbate their toxicity and amyloidogenic potential, unless tightly controlled. We reported magnetothermal stimulation as a non-invasive approach to disaggregate Aβ plaques into smaller fragments. This approach functions by generating localized, nanoscale heat on the surface of magnetic nanoparticles (MNPs) bound to Aβ plaques under a remote alternating magnetic field (AMF). Despite efficiently disaggregating Aβ plaques, the structure and fate of Aβ fragmented

by magnetothermal (MNP/AMF) stimulation remain to be elucidated. Understanding the balance between structural remodeling and phagocytic clearance is critical to optimizing therapeutic outcomes of anti-Aβ therapy. The objective of this study is to characterize the secondary structure of magnetothermally disaggregated Aβ and determine its susceptibility to microglia-mediated uptake and clearance. Our dynamic light scattering analysis revealed that MNP/AMF stimulation at a mild thermal dose reduced Aβ plaque size by ~77% (2429 ±1981 nm for control, 537 ± 136 nm for MNP/AMF group). Interestingly, Aβ fragments preserved high thioflavin T signal, suggesting retention of β-sheet-rich fibrillar structure. TEM analysis further revealed their structural distinction from soluble, oligomeric Aβ; while their cellular toxicity against human C20 microglia was comparable to intact Aβ plaques, assessed by MTT assay. We next examined whether MNP/AMF stimulation affects their susceptibility to microglia-mediated uptake and clearance. The uptake of MNP/AMF-fragmented Aβ was enhanced 5-fold in C20 microglia compared to intact Aβ plaques, which was associated with increased clearance of intracellular Aβ. This clearance was validated *in vivo* using 5xFAD mice, where mouse hippocampi were stimulated by MNP/AMF and overall Aβ burden was quantified by immunofluorescence. The application of MNP/AMF significantly reduced overall Aβ burden by ~69% (6E10 antibody). Interestingly, this reduction in Aβ burden was associated with decreased fibrillar Aβ content (~66% reduction quantified by OC antibody). Our findings support that mild magnetothermal stimulation can be successfully applied as an anti-Aβ approach by disaggregating large Aβ plaques into smaller, fibrillar fragments, rendering them more susceptible to microglia-mediated digestion and clearance.

Disclosures: M. Naveed: None. **M. Puleo:** None. **M. Kim:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

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Presentation Number: NANO48.05

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

Support: Cure Alzheimer’s Fund (to D.Y.K., and R.E.T.)
Freedom Together Foundation (to R.E.T.)
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5R37MH060009 (to R.E.T.)
1R01AG082093-01 (to D.Y.K)
NIA and McKnight Brain Research Foundation through 1U19AG073172-01 (to D.Y.K)

Title: Mitochondrial Restoration Prevents Neurodegeneration in a Novel 3D Inducible Human Brain Organoid Model of Alzheimer's Disease

Authors: *M. HEBISCH[1], T. KALATTURU[3], S. KWAK[4], S. T. WONG[5], J. PARK[2], R. E. TANZI[3], D. KIM[6];
[2]Genet. and Aging Res. Unit, [1]Massachusetts Gen. Hosp., Charlestown, MA; [4]Genet. and Aging Res. Unit, [3]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA; [5]Systems Med. and Bioengineering, Houston Methodist Res. Inst., Houston, TX; [6]Genet. and Aging Res. Unit, MIND, Massachusetts Gen. Hospital/ Harvard Med. Sch., Charlestown, MA

Abstract: The ATN framework of Alzheimer's disease (AD) describes a pathogenic cascade of amyloid-β (Aβ) accumulation, tau tangle pathology, and neurodegeneration. This sequence is triggered by pathogenic Aβ species, such as Aβ42, accumulating in brain parenchyma and eventually leads to neuronal loss. Yet, human and rodent models fail to comprehensively reproduce this Aβ42-induced neurodegeneration and formation of phospho-tau tangles. Here, we present a human iPSC-derived cerebral organoid (CO) model that enables isoform-specific, inducible expression of Aβ42 or Aβ40 (iAβ42- and iAβ40-COs) via doxycycline-regulated expression of the amyloid precursor protein (APP) containing transmembrane domain mutations. This system avoids developmental perturbations and non-Aβ cleavage products of the amyloid precursor protein (APP), and directly compares the impact of Aβ42 versus Aβ40 and an elevated Aβ42:Aβ40 ratio. iAβ42-COs comprehensively develop key AD hallmarks, including Congo red-positive amyloid plaques, tau hyperphosphorylation and paired helical filaments, and robust Aβ42-specific neurodegeneration. These hallmarks are absent in iAβ40-COs and non-transgenic control COs. Electron microscopy revealed necrotic cell bodies with granulovacuolar degeneration-like structures as well as widespread mitochondrial abnormalities exclusively in iAβ42-COs. Confocal imaging detected early accumulation of defective mitochondria lacking mitochondrial DNA. Moreover, single-cell RNA-seq analysis highlighted pathways connected to mitochondrial dysfunction in both neurons and astrocytes, as well as activation of cell stress/death-related pathways. Remarkably, treatment with a USP30 inhibitor - a mitophagy enhancer currently in clinical trials for Parkinson's disease - fully rescued mitochondrial defects and prevented Aβ42-induced neuronal loss despite the persistence of amyloid deposits. In summary, our inducible 3D brain organoid model of AD faithfully recapitulates ATN pathologies, including neurodegeneration, reveals mitochondrial dysfunction as a key mediator of Aβ42-induced neurodegeneration, and validates mitochondrial restoration via mitophagy enhancement as a promising therapeutic strategy for AD.

Disclosures: M. Hebisch: None. **T. Kalatturu:** None. **S. Kwak:** None. **S.T. Wong:** None. **J. Park:** None. **R.E. Tanzi:** None. **D. Kim:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.06

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

Support: NIA U54 AG054345
NIA R44 AG084491

Title: Utility of the APP^{SAA}knock-in mouse model of Alzheimer's disease for preclinical testing.

Authors: *L. J. SLOAN[1], D. GARCEAU[2], N. RYAN[2], J. POMEROY-TUCK[2], R. CHIDAMBARAM[3], T. RAGAN[3], R. PANDEY[2], E. BLOSS[2], G. W. CARTER[2], A. OBLAK[4], M. SASNER[2];
[1]Jackson Lab., Bar Harbor, ME; [2]The Jackson Lab., Bar Harbor, ME; [3]TissueVision, Newton, MA; [4]Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: The knock-in APP^{SAA} mouse model was developed as an alternative to transgenic APP models of familial Alzheimer's disease, which have innumerable confounding artifacts. Previously published data showed the APP^{SAA} model develops significant amyloid pathology and dysregulated neuroinflammatory signaling (Xia et al, 2022). Here, we extend age-dependent neuropathological characterization and add brain transcriptomic and plasma biomarker data to document AD-associated pathology in this pre-clinical model.
Whole-brain plaque volume was quantified using the TissueVision Marinus MP Serial Two-Photon Plus imaging platform. Plaque pathology appears in APP^{SAA} mice by 4-months in a non-sex-specific manner, primarily parenchymal, with Aβ-associated proteins like LAMP1, IBA-1, and GFAP present at this age. Plaques are deposited in a linear pattern until 12-months when accumulation plateaus until 19-months-of-age, with the highest plaque burden in the hippocampus. Quantitative analysis of soluble and insoluble Aβ species in the brain was performed using an MSD 6E10 kit. From 4- to 12-months-of-age, APP^{SAA} mice show an age-dependent increase in both soluble and insoluble levels of $A\beta_{40}$ and $A\beta_{42}$. At 12-months-of-age, pathways from CA1 to medial prefrontal cortex demonstrated robust synaptic loss that was exacerbated in proximity to plaques. At the same age, APP^{SAA} mice exhibit deficits in fear conditioning behavior.
Bulk hemi-brain transcriptomic data shows an age-dependent alignment of APP^{SAA} mice to clinical human data in the AMP-AD modules. While there is minimal alignment at 4-months-of-age between AMP-AD modules and APP^{SAA} mice, by 12-months the transcriptomic signature resembles that of a 4-month-old 5xFAD mouse. Lastly, the Alamar NULISA 120 CNS mouse panel revealed that pTau-T217 is the most strongly affected plasma protein by age and genotype in APP^{SAA} mice and is strongly correlated with SNAP25 and TARDP.
These results demonstrate that the APP^{SAA} knock-in model serves as useful preclinical model for studying disease mechanisms and for testing of therapeutic strategies targeting amyloid, tau, or neuroinflammatory mechanisms. Moreover, the APP^{SAA} model shows disease progression that more closely models AD in humans compared to transgenic models.

Disclosures: L.J. Sloan: None. **D. Garceau:** None. **N. Ryan:** None. **J. Pomeroy-Tuck:** None. **R. Chidambaram:** None. **T. Ragan:** None. **R. Pandey:** None. **E. Bloss:** None. **G.W. Carter:** None. **A. Oblak:** None. **M. Sasner:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.07

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

Support: NIH Grant AG068215
Lyman T Johnson Fellowship
R41AG082600

Title: Low-Frequency Mechanosensory Stimulation Promotes Sleep and Enhances Slow-Wave Activity in a Mouse Model of Alzheimer's Disease

Authors: *G. MORILLO SEGOVIA[1], D. HUFFMAN[4], M. P. MURPHY[2], A. D. BACHSTETTER[5], M. J. DUNCAN[6], B. F. O'HARA[3,4], S. SUNDERAM[1];
[1]Biomed. Engin., [2]Mol. and Cell. Biochem., [3]Univ. of Kentucky, Lexington, KY; [4]Signal Solutions, LLC USA, Lexington, KY; [5]Adam Bachstetter, Lexington, KY; [6]Neurosci., Univ. of Kentucky Med. Sch., Lexington, KY

Abstract: Sleep is critical for brain function and cognitive health, contributing to the clearance of neurotoxic metabolites such as amyloid β (Aβ), a hallmark of Alzheimer's disease (AD). Slow wave activity (SWA), a defining feature of deep sleep, supports these processes by promoting coordinated neuronal activity and metabolic waste clearance, suggesting SWA modulation may be a viable strategy to mitigate AD pathology. Acoustic, visual and vestibular stimulation have been shown to promote sleep and enhance SWA in AD mouse models. However, vibrotactile stimulation remains understudied as a strategy to enhance SWA. In a pilot crossover study, we evaluated low frequency amplitude-modulated vibrotactile stimulation at four different frequencies using MouseQwake cages (Signal Solutions, LLC) in AD mice to identify parameters that enhance sleep without disruption. Stimulation at 1 Hz continuously across four intervals (ZT 2-3, 4.5-5.5, 7-8, 9.5-10.5) for 3 days increased total sleep during the light phase relative to baseline. Spectral analysis showed increased 1 Hz power and a modest elevation in relative delta power during NREM sleep, suggesting entrainment. Hence, 1 Hz stimulation at a device intensity setting of 1V was selected for longitudinal testing. To evaluate the effects of chronic stimulation, we used electroencephalography (EEG) and electromyography (EMG) in APP/PS1 knock-in mice (10 months, N=5 per group, sex-balanced). After baseline, animals were assigned to sham or stimulation conditions and recorded for 2 weeks. Stimulation was delivered daily during the same four light phase intervals. Sleep was scored in 4-second epochs using machine learning on EEG/EMG features and verified manually. Preliminary results show that stimulated animals slept ~10% more per day and 8% more during the light phase than controls during treatment weeks, with no changes during the dark phase. While NREM and REM bout durations over the light phase were unchanged, mean sleep bout duration increased by over 40% in both weeks, suggesting better consolidated sleep during stimulation periods. Spectral power at 1 Hz was elevated during NREM sleep in stimulation blocks, indicating entrainment of slow oscillations. Following recordings, animals were sacrificed at ZT15 for tissue collection. Ongoing analyses include immunohistochemistry for Aβ and microglia, and biochemical quantification of soluble and insoluble forms of Aβ in cortex and hippocampus. These results

indicate that low frequency vibrotactile stimulation enhances sleep and entrains SWA in APP/PS1 mice, supporting its potential as a noninvasive sleep modulation strategy.

Disclosures: G. Morillo Segovia: None. **D. Huffman:** None. **M.P. Murphy:** None. **A.D. Bachstetter:** None. **M.J. Duncan:** None. **B.F. O'Hara:** None. **S. Sunderam:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.08

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

Support: NIH-R01-AG076129

Title: 5xFAD transgene blocks age-related changes to sleep important for memory but not circadian rhythm in recombinant inbred AD-BXD panel

Authors: *J. A. KRAVCHENKO[1], B. KEENAN[2], B. SACONI[2], X. GUO[2], S. SHEMKE[1], B. MACDONALD[1], T. J. HOHMAN[3], C. C. KACZOROWSKI[4];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Vanderbilt Univ. Med. Ctr., Nashville, TN; [4]Neurol., The Univ. of Michigan, Ann Arbor, MI

Abstract: Introduction: Sleep and circadian rhythm disturbances can precede cognitive decline in Alzheimer's disease (AD) and related dementias by upwards of 20 years. Characterizing these disruptions and how they drive AD memory impairment will reveal both novel biomarkers and therapeutic options to delay or even prevent AD onset. While many studies have revealed associations with sleep and AD cognitive outcomes in the clinic, there is limited ability to model the genetic heterogeneity in the human population while causally testing these relationships *in vivo*. To address this, we characterized sleep/wake and circadian rhythm in a recombinant inbred mouse panel carrying the 5xFAD transgene (AD-BXDs) known to model cognitive impairment in human AD. **Methods:** Male and female mice from 28 strains of the AD-BXD panel carrying the 5xFAD transgene (n=359) and non-transgenic (Ntg) littermate controls (n=369) completed sleep/wake phenotyping (5 days 12:12 LD) and circadian phenotyping via voluntary wheel running (7 days 12:12 LD, 10 days DD). Sleep and circadian phenotyping were followed up with contextual fear conditioning to evaluate memory. Cohorts were cross-sectional, with strains tested at 6 and 14 months of age. **Results:** Female AD-BXDs at 14 months showed impairments to memory acquisition (p=8.12e-8) and recall (p=7.23e-5) relative to 6-month-old counterparts. Ntg-BXDs and males did not show memory deficits, in-line with previous AD-BXD studies. Overall, we observed that Ntg-BXDs of both sexes slept more with age (Males p=0.015; Females p=8.54e-7), while AD-BXDs slept less with age (Males p=0.013; Females p=0.002). During circadian phenotyping, Ntg and AD-BXDs showed similar changes to amplitude, intradaily variability (IV), and interdaily stability with age. We observed a robust positive relationship between IV at 6 months and contextual fear recall at 14 months, but only in female AD-BXDs

(R=0.56, p=0.0043). **Conclusion:** Normal aging is characterized by changes to sleep and circadian rhythm but not memory. Presence of the 5xFAD transgene impairs age-related changes to sleep and memory but not circadian rhythm. Our findings suggest that intradaily variability could serve as a predictor of AD cognitive outcomes. Overall, our results demonstrate that the AD-BXD panel exhibits 5xFAD and age-related changes to sleep and circadian rhythm that may influence memory. Future work aims to confirm our findings via polysomnography of select AD-BXD strains and to perform forward genetic mapping to identify genetic modifiers of IV that may be used to modify AD cognition.

Disclosures: J.A. Kravchenko: None. **B. Keenan:** None. **B. Saconi:** None. **X. Guo:** None. **S. Shemke:** None. **B. Macdonald:** None. **T.J. Hohman:** None. **C.C. Kaczorowski:** None.

Nanosymposium

NANO48: Alzheimer's Disease Therapeutic Strategies: Amyloidosis Models

Location: WCC Rm 201

Time: Wednesday, November 18, 2026, 1:00 PM - 3:15 PM

Presentation Number: NANO48.09

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

Support: Ministry of Education (RS-2025-25423183)
Ministry of Health & Welfare (HU22C0150)
Ministry of Science & ICT (NRF-2022R1A2C3009749)
Institute of Basic Science Grant (IBS-R001-D2)

Title: 40-Hz Auditory Stimulation Restores Astrocytic Ca^{2+} Influx and Improves Sleep Disturbances in Alzheimer’s Disease

Authors: *M. PARK[1], M. BHALLA[3], J. JOO[3], C. CHEONG[2], C. LEE[3], T. KIM[2];
[1]Gwangju Inst. of Sci. and Technol., Buk-gu, Korea, Republic of; [2]Gwangju Inst. of Sci. and Technol., Gwangju, Korea, Republic of; [3]Ctr. for Cognition and Sociality, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Alzheimer’s disease (AD) is characterized by amyloid-beta (Aβ) accumulation and sleep disturbances. Previous studies reported that Aβ accumulation and sleep disturbances in AD form a positive feedback loop and impaired Ca^{2+} influx and volume transient in astrocytes. Reactive astrocytes in AD exhibit aberrant GABA production, impaired calcium signaling, and dysfunctional homeostatic properties. Sensory stimulation at 40 Hz showed therapeutic impacts on AD. However, whether astrocytes mediate the therapeutic effects of 40-Hz sensory stimulation on sleep disturbances remains unknown. We hypothesized that 40-Hz auditory stimulation could ameliorate sleep disturbances by enhancing the astrocytic Ca^{2+} influx. We used 6-month-old male 5xFAD mice as an AD model. Two-hour daily 40-Hz auditory stimulation or white noise was applied for two-weeks. We recorded the 24-hour electroencephalographic (EEG) for sleep-wake analysis in pre- and post-stimulation days. Cortical nNOS neurons were labeled with AAV-nNOS-eGFP, and tonic GABA currents were measured by patch-clamp recording.

Astrocytic Ca^{2+} signals and cell volume transients were assessed using GCaMP6f and intrinsic optical signals. AQP4 was suppressed via AAV-PHP.eB-pSicoR-shAQP4-mCherry injection, and astrocytic Ca^{2+} influx was optogenetically enhanced using AAV-PHP.eB-GFAP-FLAG-monSTIM1, a blue-light-activated Ca2+ channel. AD pathology and reactive astrocytes were evaluated by immunohistochemistry, and transcript levels were quantified by qRT-PCR. rASSR reduced astrocytic GABA-mediated inhibition of nNOS-expressing, sleep-promoting cortical neurons. Additionally, rASSR enhanced neuronal activity-induced cell volume transients and Ca^{2+} influx in astrocytes, which subsequently decreased Maob expression and increased Nrf2 expression. Suppression of AQP4 diminished the therapeutic effects of rASSR. Optogenetic enhancement of astrocytic Ca^{2+} influx via monSTIM1 recapitulated the therapeutic effects of rASSR. Our findings suggest that 40-Hz rASSR ameliorates Aβ pathology and sleep disturbances by restoring astrocytic Ca^{2+} influx through an AQP4-dependent mechanism, which suppresses astrocytic GABA-mediated inhibition of nNOS-expressing neurons and reduces Aβ burden.

Disclosures: M. Park: None. **M. Bhalla:** None. **J. Joo:** None. **C. cheong:** None. **C. Lee:** None. **T. Kim:** None.

Nanosymposium

NANO49: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Rm 145

Time: Wednesday, November 18, 2026, 1:00 PM - 4:30 PM

Presentation Number: NANO49.01

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01DC002390

Title: Rapid central reafference suppression of vestibular prosthetic input during voluntary gaze shifts

Authors: *A. CHHABRA, O. M. LEAVITT BROWN, K. WIBOONSAKSAKUL, K. E. CULLEN;
Biomed. Engin., The Johns Hopkins Univ., Baltimore, MD

Abstract: The brain must differentiate between externally generated and self-generated sensory inputs in order to maintain perceptual stability and generate accurate motor behavior. Despite recent advances in neuroprostheses, little is known about how central circuits interpret prosthetic sensory signals, particularly when they are self-generated. For vestibular prosthesis users, the brain must learn to utilize artificial vestibular input when beneficial while suppressing it when it conflicts with behavioral goals. Here, we investigated how vestibular nuclei neurons adapt to self-generated prosthetic stimulation during a voluntary gaze-shift task. Bilateral vestibular loss (BVL) monkeys implanted with a multichannel vestibular prosthesis were trained to perform voluntary gaze shifts while neural activity was recorded using a high-density Neuropixels probe in the vestibular nuclei. Animals received baseline prosthetic stimulation (150 pulses/s) followed

by head-velocity-modulated prosthetic stimulation. We focused on vestibular-only (VO) neurons, which normally exhibit cerebellar internal model based reafference cancellation during self-generated movements. In the absence of natural vestibular input, neurons displayed little modulation during either active or passive head movements. Following introduction of head-velocity-modulated prosthetic stimulation, robust neural modulation emerged during passive head movements. During active gaze shifts, however, neurons initially encoded the prosthetic input as though it were externally generated. Over approximately 80 trials, adaptive learning occurred and reafference suppression progressively emerged across the recorded population (n=7). Together, these findings demonstrate rapid context-dependent central adaptation to prosthetic vestibular input after initial disruption and provide strong support for the hypothesis that artificial vestibular signals can be integrated into vestibular pathways in a manner resembling natural vestibular feedback.

Disclosures: A. Chhabra: None. **O.M. Leavitt Brown:** None. **K. Wiboonsaksakul:** None. **K.E. Cullen:** None.

Nanosymposium

NANO49: Neuroprosthetics: Non-Motor Interfaces

Location: WCC Rm 145

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Presentation Number: NANO49.02

Topic: F.05. Brain-Machine Interface

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Title: Phosphene generation for the third recipient of the Intracortical Visual Prosthesis (ICVP)

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Abstract: The Intracortical Visual Prosthesis (ICVP) has previously been used to produce basic artificial vision in two blind humans with bare light perception. A third participant with no light perception has now been implanted with the ICVP and initial attempts at phosphene generation have been completed. The ICVP electrically stimulates the visual system via wireless floating microelectrode arrays (WFMAs) that are implanted subdurally into cortex. Each WFMA has 16 1.3-1.6 mm stimulating electrodes. The first, second, and third participants received 25, 32, and

34 WFMAs, respectively. All implantations were performed on the right dorsolateral occipital lobe. Implantation for the third participant was planned based on experiences with the first two participants and anatomical T1 MRI data. Visual area boundaries were estimated using models of retinotopy applied to flattened cortical surface representations. The third participant's WFMAs were implanted approximately 6-56 mm superior to the occipital pole and 9-39 mm right of the midline, prioritizing accessible portions of V1-V3. No complications were encountered during the surgery or the immediate follow-up period. All of the third participant's 544 electrodes were able to stimulate using pulses with 200 μs cathodic phases and current with limits of 40-70 μA at 39 days after implantation. To assess phosphene generation potential, sets of 4-8 adjacent electrodes on each WFMA first stimulated with 500 ms trains of biphasic, cathodic-first pulses with 200 μs, 10 μA cathodic phases with randomized interpulse intervals averaging 5.5 ms. Three trains were presented in quick succession with auditory cues to help the participant distinguish electrically elicited phosphenes from Charles Bonnet hallucinations and other visual noise. If no phosphenes were reported, current was increased in steps of 10 μA until stimulation limits were reached. Phosphenes in the left visual field were reported from this pattern of stimulation for nine WFMAs along the central medial portion of the implanted area, estimated to be in cortical areas V2-V3A. Giving the participant control of stimulation via a button further helped differentiate ICVP phosphenes from noise and allowed detection of phosphenes from four additional WFMAs, three inferior and one superior to the first nine, for a total of 13 phosphene-producing WFMAs. Five WFMAs produced phosphenes with groups of four electrodes using 30-50 μA and eight WFMAs used groups of eight electrodes with 12-55 μA per electrode. Testing will continue with this participant to assess use of these phosphenes for artificial vision and to compare experiences against those of previous participants.

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Nanosymposium

NANO49: Neuroprosthetics: Non-Motor Interfaces

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Topic: F.05. Brain-Machine Interface

Support: NIDCD F31-DC020390
NIDCD R01-DC002390

Title: Biomimetic vestibular prosthetic stimulation improves restoration of postural control

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Abstract: Bilateral vestibular loss (BVL) causes imbalance and increased fall risk, yet current vestibular prostheses use conventional stimulation paradigms that do not capture the physiological complexity of natural vestibular encoding. Natural vestibular afferents exhibit response properties classified as regular or irregular based on resting rate regularity, with irregular afferents showing phasic, acceleration-sensitive dynamics ideally suited for balance control and providing the major input to vestibulospinal reflex pathways. We hypothesized that biomimetic stimulation reproducing irregular afferent dynamics would better restore postural control than conventional approaches.

We tested postural responses to platform tilts in two rhesus monkeys with BVL and unilateral vestibular prostheses targeting the anterior semicircular canal. BVL caused profound deficits in head stability, including a 5-fold increase in head velocity range, increased acceleration variability, head motion opposite the compensatory direction, and reduced center-of-pressure responses—consistent with impaired vestibulocollic and vestibulospinal reflexes. We compared 3 stimulation paradigms: static baseline stimulation, biomimetic regular stimulation mimicking regular afferent dynamics, and biomimetic irregular stimulation mimicking irregular afferent dynamics.

Static stimulation produced minimal and slow improvements in postural responses. When we shifted to biomimetic mappings, stimulating with regular afferent dynamics led to more rapid improvements, but of similar magnitude to static. Importantly, stimulating with irregular afferent dynamics produced the most rapid and substantial restoration of postural control, with head velocity responses close to normal, reduced acceleration variability, and robust compensatory center-of-pressure responses. For example, irregular stimulation was associated with a 60% reduction in head velocity range, compared to 20% for static. Direct comparison across paradigms revealed that irregular stimulation consistently outperformed both static and regular stimulation across all postural measures in both animals.

Together, these findings identify irregular afferent-like dynamics as a key design principle for restoring balance-relevant sensorimotor control after vestibular loss and highlight a broader principle for biomimetic sensory prostheses: effective restoration may depend on recreating the behaviorally relevant dynamics of natural neural codes rather than simply providing sensory drive.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

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Blackrock Neurotech Contract to West Virginia University
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Title: Stimulation stability and intraoperative evaluation of the Auditory Nerve Implant

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Abstract: Cochlear implants are the exemplar neuroprosthetic technology, having provided meaningful hearing and communications restoration to >1 million patients. CIs are implanted in children 6 months or older, usually providing decades of hearing restoration, setting a high bar for both the lifetime and performance. But CI performance for challenging tasks such as speech in noise, low frequency percepts, and in expanding the pool of independent frequency channels has not improved in more than two decades. Lack of improvement has been attributed to the difficulty in stimulating the nerve through the bony wall of the cochlea with intracochlear electrodes. Our approach to improve hearing prostheses is to place a Blackrock Neurotech penetrating microelectrode array in the auditory nerve near the cochlea connected to a MEDEL Synchrony 2 cochlear stimulator forming the Auditory Nerve Interface device. The objective is to evaluate the benefits of direct and focal auditory nerve microstimulation in perceptual studies with human subjects in Hannover Germany. Stimulation stability testing was performed with five fully integrated devices using 6.3 billion pulses at 100 µA and 1200 µA, representing the maximum clinical pulse and stimulator pulse intensities. Longitudinal impedances combined with optical and electron microscopy found the electrodes tolerated stimulation without observed degradation. A first-in-human intraoperative study with nine volunteers was performed under Ethics Committee approval at the Hannover Medical School. Study participants received tumor resection surgeries by a translabyrinthine approach, the same surgical approach used to place ANI electrodes. We evaluated the surgical approach, electrode placement, evoked auditory brainstem responses (eABRs), and electrode impedances with a wired version of the electrode array. Evoked responses were measured with estimated stimulation thresholds between 20 and 40 µA demonstrating surgical and technology viability. A forward masking paradigm was used

evaluate independence of percepts evoked by different electrodes, and provided evidence of distinct nerve fiber pools recruited. Pre-clinical cat model studies with 3-month endpoints involving periodic stimulation, evaluation eABRs, and electrode impedance measurements were also completed. Sustained eABRs and electrode impedances <70 kΩ support the sustained nerve health and device performance over clinically relevant periods. In conclusion, these data support the ANI device is sufficiently safe and effective to initiate perceptual testing in a clinical investigation.

Disclosures: L. Rieth: 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.; lackrock Neurotech. **T. Stump:** None. **I. Sondh:** None. **K. Dyballa:** None. **M. Leber:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **J. Crew:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **K. Huebner:** A. Employment/Salary (full or part-time):; MEDEL. **A.P. Heiller:** None. **W. Nogueira:** None. **L.A. Johnson:** None. **G.M. Ghose:** None. **W.M. Thomas:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **H.A. Holman:** None. **R. Gurgel:** None. **D.J. Warren:** None. **S. Zuniga:** None. **A. Loveland:** None. **R. Franklin:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **A. Samii:** None. **A.J. Oxenham:** None. **S.B. Strahl:** A. Employment/Salary (full or part-time):; MEDEL. **F. Solzbacher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Neurotech. **M. Adams:** None. **T. Lenarz:** None. **H.H. Lim:** 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.; Blackrock Neurotech.

Nanosymposium

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Topic: F.05. Brain-Machine Interface

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Title: Peripheral nerve stimulation modulates anticipatory postural adjustments after lower limb loss

Authors: *E. PETROS[1,2], H. CHARKHKAR[1,2];
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Abstract: Gait initiation is characterized by anticipatory postural adjustments (APAs). During an APA the body's center of pressure (CoP) shifts from the swing limb to the stance limb to prepare for a step. Somatosensation is critical here, signaling foot contact and the transfer of body weight across the base of support. For individuals with lower limb loss (LLL), the prosthetic foot provides no such information, disrupting APAs. The intact limb compensates, producing longer APAs and greater loading on that side. A sensory neuroprosthesis (SNP) providing somatosensory feedback via peripheral nerve stimulation could alleviate these deficits. The SNP utilizes high density cuff electrodes implanted on the sciatic and tibial nerves in the residual limbs of individuals with LLL. Electrical stimulation of the nerves via this interface elicits plantar sensations perceived as originating from the missing limb. The SNP maps these sensations to the pressure distribution under the prosthetic foot to provide real-time feedback on prosthesis-floor interactions during standing and walking. We evaluated the SNP's effect on gait initiation in three individuals with LLL (LL1 and LL2 transtibial, LL3 transfemoral). We prompted participants to initiate gait with a left or right step via a visual cue and measured the CoP with force plates. To assess response time and the speed of weight shifting to each foot, we calculated the duration of three phases: reaction, release, and unloading. These phases were defined respectively as cue to APA onset, APA onset to maximum lateral displacement toward the stepping foot, and maximum lateral displacement to swing foot toe off. We analyzed the effect of SNP and stepping side on phase durations with a two-way ANOVA and Tukey post-hoc tests. All participants showed distinct CoP trajectories between stepping sides with intact steps resulting in greater anterior excursion. Participants LL1 and LL2 exhibited longer release times for intact side steps by 0.097 and 0.072 seconds, respectively (LL1 $p < 0.001$, LL2 $p < 0.05$). Unloading times on the intact side were also longer for LL1 by 0.083 and LL2 by 0.084 seconds (LL1, LL2 $p < 0.001$). For SNP effects, LL2's reaction times were longer by 0.074 seconds with the SNP active ($p < 0.05$). LL3 had a significant interaction effect between side and SNP ($p < 0.01$). Notably, with SNP active, unloading time for intact steps decreased by 0.052 seconds ($p < 0.05$). These results indicate the SNP did not alter APA phase durations for our transtibial participants. However, the SNP did facilitate weight transfer onto the prosthetic limb in the transfemoral participant, suggesting possible benefits for people with higher deficits.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

Title: Non-Invasive Sensory Neuroprosthesis Produces Sensations in the Missing Foot of a Participant with Lower-Limb Amputation

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Abstract: Spinal cord stimulation (SCS) can be utilized to produce artificial sensations in the missing limbs of individuals with amputation, providing sensory feedback during walking and improving balance and postural control (Nanivadekar et al., 2023). SCS can be achieved using implanted electrodes in the epidural space. Although effective, implanted SCS methods present accessibility limitations for individuals who are not eligible or cannot access surgery. Thus, it is necessary to investigate non-invasive alternatives to provide repeatable, comfortable sensory feedback. Here, we explore the use of transcutaneous spinal cord stimulation (tSCS) in a participant with a unilateral, transtibial amputation to restore sensory feedback from a missing limb. tSCS uses adhesive surface electrodes over the spine to target similar neural structures as SCS implants without the need for surgery. In this study, we explored the resolution of sensations achievable in the missing foot with tSCS using classical psychophysical tests, determined the range of sensory percepts and locations through sensory mapping and descriptions, and performed balance and gait tasks with real-time sensory feedback from tSCS. All amplitudes for sensory mapping were tested at 30, 50, 80, and 100 Hz. Sensory thresholds ranged from 9-11 mA over the four days of testing, with a maximum comfortable amplitude of 18-20 mA. The just-noticeable difference in frequency was 5.06 Hz at a 50 Hz reference, and the perceived intensity increased with a slope of 1.02 over a range of 5-100 Hz. Sensations were reliably achieved on the toes, ball of the foot, lateral sole, and lateral malleolus of the missing limb. Sensations were primarily described as “tugging”, “static”, or “tapping” across the range of amplitudes and frequencies. When tSCS was time-aligned with the participant’s prosthetic limb loading during the gait cycle using an underfoot pressure sensor, real-time, somatotopic sensory feedback was provided during a narrowing beam dynamic balance task. Without sensory feedback, the participant travelled 168 ± 8.5 cm on the narrowing beam. With sensory feedback, they achieved an average distance of 171 ± 30.4 cm. Although these differences do not meet the requirement for a minimal detectable change (> 4.88 cm), the participant noted that sensory feedback made them feel “more confident in trusting [their] prosthesis”, and that they enjoyed the sensation of being able to “feel” their foot during walking. These findings can help guide the implementation of more intuitive, accessible sensory neuroprostheses, providing prosthetic users with an increased sense of embodiment, ownership, and control of their prosthesis.

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Title: Restoration of multimodal thermo-tactile sensation in upper-limb amputees

Authors: *J. MUHEIM[1], F. LEONG[3], M. LASFARGUES[1], S. MICERA[4], S. SHOKUR[2]; [1]EPFL, Geneva, Switzerland; [2]STI, EPFL, Genève, Switzerland; [3]Neuro-X, EPFL, Nyon, Switzerland; [4]Swiss Federal Inst. of Technol., Lausanne, Switzerland

Abstract: Limb loss profoundly alters somatosensory experience, impairing motor control, body ownership, and quality of life. To date, sensory restoration for prosthetic limb users has remained largely unimodal, focusing on the independent delivery of force, proprioceptive, thermal, or nociceptive feedback. Natural touch is intrinsically multimodal: object interactions simultaneously convey tactile and thermal information but current solutions are not able to provide this. Here, we address this issue with a fully non-invasive, wearable cutaneous interface capable of delivering combined cold, warm, and electrotactile stimulation in a single compact device, bringing multimodal feedback within reach outside the laboratory.
Psychophysical evaluation in healthy participants demonstrated that concurrent stimulation elicited accurate and graded percepts across both thermal and tactile modalities. Cross-modal interactions were present, although modest: thermal perception was slightly reduced during concurrent transcutaneous electrical nerve stimulation (TENS), particularly for cold stimuli, while temporal integration enabled both modalities to be perceived as simultaneous within a defined onset-delay window. In several stimulus pairings, the complementary modality also improved reaction times—TENS accelerated the detection of warm stimuli, whereas both cold and warm stimulation enhanced response speed to TENS.
To assess the translational potential of this approach, we systematically mapped residual-limb skin in six individuals with transradial amputation. We observed substantial spatial overlap between tactile, cold, and warm phantom hand projections: when tactile projection sites were present, cold sensations co-localized in 77% of cases, and all three modalities converged in 43%. Finally, in a real-time object discrimination task, four amputees reliably identified six object categories defined by combined stiffness and temperature cues (accuracy 0.70-0.87; chance level = 0.17). Together, these findings establish a framework for multimodal sensory neuroprosthetics, demonstrating that thermotactile feedback can be spatially encoded, perceptually integrated, and functionally exploited. The approach defines a concrete path toward prosthetic systems capable of restoring the full somatosensory texture of embodied experience.

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Title: Evoked Phantom Limb Sensations through Sciatic Nerve Regenerative Peripheral Nerve Interfaces in an Individual with Transfemoral Amputation

Authors: *H. RAZAVI[1], J. KANETIS[2], B. PERLIN[2], C. A. CHESTEK[3], P. CEDERNA[4], T. A. KUNG[4], D. GATES[5];
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Abstract: Individuals with transfemoral amputation (TFA) lack sensory feedback from the missing limb, contributing to impaired function and reduced prosthesis embodiment. Regenerative Peripheral Nerve Interfaces (RPNIs) are biological constructs created by implanting residual peripheral nerves into free muscle grafts. While RPNI stimulation evokes referred sensations after upper-limb amputation, its application in lower-limb amputation remains unexplored. This first-in-human study examined the location, stability, and integration of sensations evoked through sciatic nerve RPNIs in an individual with TFA.A 56-year-old man with TFA underwent creation of five sciatic nerve RPNIs with intramuscular electrodes (Synapse Biomedical) under FDA IDE (G230230) and IRB approval (HUM00235849). Sensation maps were characterized during stimulation of individual RPNIs and monitored longitudinally. Sensations evoked by simultaneous stimulation of multiple RPNIs were also assessed. As a preliminary evaluation of functional utility, the participant completed standing balance trials on foam with and without sensory feedback delivered through an RPNI that elicited sensation on the medial plantar surface of the phantom foot.Stimulation of all five RPNIs evoked localized sensations referred to distinct regions of the phantom lower limb and foot. These sensation maps remained relatively stable over approximately one year. Simultaneous stimulation of two RPNIs produced a single integrated percept combining the referred locations of each RPNI rather than two separate sensations. During standing balance testing, sensory feedback did not reduce postural sway and was associated with larger 95% center-of-pressure ellipse areas during both eyes-open and eyes-closed conditions. Throughout the study, the participant perceived the phantom knee as flexed at approximately 90°, creating a persistent mismatch between phantom limb perception and prosthetic alignment.This study demonstrates that stimulation of sciatic

nerve RPNIs can evoke stable, localized sensations referred to the phantom lower limb and foot over one year after implantation. Furthermore, simultaneous stimulation of multiple RPNIs may enable richer sensory percepts through cross-channel integration. Although immediate functional benefits were not observed during standing balance, adaptation to novel sensory feedback may require training and improved alignment between phantom limb perception and prosthetic position. Future work will investigate multi-channel stimulation, long-term sensory training, and performance during tasks that rely more heavily on lower-limb sensory feedback.

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Title: Long-term Stability of Sensory Percepts following Regenerative Peripheral Nerve Interface Surgery after Upper-Limb Amputation

Authors: *S. KERSTENS[1], O. LEE[2], D. M. WALLACE[5], C. NWOKEABIA[1], P. CEDERNA[1], C. A. CHESTEK[3], D. GATES[4];
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Abstract: Restoring sensory feedback after amputation is critical for achieving intuitive prosthetic limb control. While modern prostheses provide a variety of approaches to providing feedback, restoring sensations that are perceived in the phantom limb remains a significant challenge. Among recent advances in peripheral nerve interfaces, regenerative peripheral nerve interfaces (RPNIs), small free muscle grafts implanted around peripheral nerves following amputation, represent a promising solution. RPNIs form biologically stable constructs that enable bidirectional communication between the nervous system and prosthetic devices: in

addition to acting as amplifiers for efferent signals that convey motor intent, they serve as a reliable interface through which somatosensory feedback can be delivered using electrical stimulation. We have previously shown that pulsed stimulation of RPNIs evokes localized sensations referred to the phantom limb that correspond to the nerve's native dermatome and can even elicit proprioceptive sensations at higher stimulation amplitudes, such as the perceived flexion of individual phantom fingers. In addition to identifying a functional stimulation range and stimulation sensitivity, we also found that simultaneous stimulation of multiple RPNIs produces novel percepts located in regions between the perceptual areas associated with individually stimulated RPNIs. Here, we extend this work using longitudinal data from a 59-year-old female with a transradial amputation enrolled in NCT03260400, showing that RPNI-stimulation-evoked percepts remain stable for over seven years. Using hand maps representing stimulation-evoked percepts at perception threshold, we found that percepts remain anatomically consistent across time in terms of spatial location and perceptual surface area. This was true across all three RPNIs. Additionally, responses to increases in stimulation amplitude above perception threshold also suggest consistent scaling of perceived intensity over time. Ongoing data collection and analyses aim to quantify the stability of stimulation thresholds and evoked percepts over time, as well as to further investigate whether strategic stimulation of multiple RPNIs can elicit distributed sensations across the phantom hand. Together, these findings may help inform the clinical viability of leveraging long-term stimulation-evoked percepts following RPNI surgery to provide functionally relevant sensory feedback for prosthesis control.

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Topic: F.05. Brain-Machine Interface

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Title: Loaded Question: does preloading alter cutaneous afferent encoding of foot sole load patterns?

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Abstract: Cutaneous feedback from low threshold mechanoreceptors located within the glabrous skin of the foot sole provides information about the distribution and progression of load during standing and gait. This pressure is continuously shifting to support balance during both stationary and locomotor activities. Cutaneous receptor behaviour typically focuses on low to no starting load, characterising afferents into slowly adapting (SA) and fast adapting (FA) type I and II. From this understanding, FA afferents encode changes in load (including onset and offset) and SA afferents encode the changes in, and magnitude of, load. To identify the ability of different afferent classes to encode changes in load under different initial loading conditions, we loaded the foot in two loading paradigms: from an unloaded state and following preloading. Responses from 25 cutaneous afferents (15 FAI 4 SAI, 6 SAII) were recorded from the tibial nerve using microneurography. Preloading included ramps starting at different levels of initial load (1 to 15N) before increasing load at different rates (0.5 to 150N/s). We examine afferent response magnitude using peak3 instantaneous firing rate, and temporal sensitivity by assessing the time to first spike. Overall, when preloaded, there is a reduction in the number of ramps that elicit any response for FAIs. In contrast SA's continue to respond to both loading paradigms. All afferent classes maintain their ability to encode rate of loading (peak3), although the frequency is reduced with preload. FAIs exhibited the strongest correlation when controlling for starting load (both paradigms r=.45), suggesting they remain best able to encode the rate of loading. When initially unloaded, the rate of loading is weakly correlated with the time to the first spike for all afferent classes. The strength of this relationship does not change significantly for SAI or SAII afferents following preloading but strengthens for FA1s (from r=-.22 to r=-.53). Together these findings suggest that at baseline, FAI firing onset encodes stimulus contact, whereas under preload spike initiation depends on loading rate, with faster rates producing earlier onset. Although preload delays FAI spike initiation, changes to load may be offset by SA responses, which are not as impacted. This shift in spike timing for FAI has important implications for motor control; if the rate of loading during gait is slow this may delay FAI firing and affect the speed of reflex-mediated changes in muscle activity. Importantly, this work highlights the need to provide both appropriate firing rates and temporally accurate information via prosthetics.

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Nanosymposium

NANO49: Neuroprosthetics: Non-Motor Interfaces

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Presentation Number: NANO49.11

Topic: F.05. Brain-Machine Interface

Support: VA RRDT Merit Review #I01 RX003699

Title: Integration of proprioceptive sensation from voluntary contraction and peripheral nerve stimulation in a participant with upper limb loss

Authors: *J. D. MUDGE[1,2], R. L. HARDESTY, Jr.[1,2], E. L. GRACZYK[1,2];
[1]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH; [2]FES Ctr., Louis Stokes Cleveland VA Med. Ctr., Cleveland, OH

Abstract: Proprioception is the body's sense of limb position, movement, and force. In people with amputation, commercial prostheses can help with performing tasks of daily living, but they lack proprioceptive feedback. This is problematic because proprioception is important for accurate control of limbs, and thus prosthesis control may never be fully intuitive without it. Prior studies using peripheral nerve stimulation (PNS) have generated distally referred sensations of proprioception, but they consisted of low range of motion (ROM) percepts compared to the natural ROM of hand joints. We hypothesize that, because peripheral nerve stimulation is unlikely to activate small fibers such as γ-motor neurons, proprioceptors within the residual muscle remain in a low sensitivity state compared to during α-γ coactivation arising from voluntary contraction (VC). In this study, we investigate the effects of combining VC with PNS on proprioceptive intensity and ROM. One male participant with unilateral transradial limb loss implanted with Composite Flat Interface Nerve Electrodes (C-FINEs) around his residual nerves rated sensations evoked by PNS and VC of his residual muscles. In each trial, 1 of 4 pulse widths (PWs) of PNS at 100 Hz were delivered to a C-FINE contact, while the participant produced 1 of 4 VC levels with the agonist or antagonist muscle. The participant rated the intensity of movement sensation and displayed ROM by matching the posture of his phantom hand with his intact hand while wearing a motion capture glove. Multiple linear regressions were conducted to assess VC and PW effects on intensity and ROM. PNS produced sensations of finger flexion. During the agonist VC experiment, PW and VC significantly increased intensity ($F(3,316)=257$, $R^2=0.73$, $P_{fit}<0.01$), but only VC influenced ROM ($F(3,316)=9.57$, $R^2=0.09$, $P_{fit}<0.01$). During the antagonist VC experiment, PW and VC significantly increased intensity ($F(3,316)=97.2$, $R^2 = 0.48$, $P_{fit}<0.01$) and ROM ($F(3,316)=7.88$, $R^2=0.07$, $P_{fit}<0.01$). For both agonist and antagonist VC intensity and ROM, the interaction of PW and VC was not significant. These results suggest that PNS did not significantly increase ROM in the agonist VC case. However, when the antagonist to the stimulated muscle was contracted, PNS did significantly increase perceived ROM. This may be because the participant's resting phantom position was a nearly closed fist, which may cause a ceiling effect where, during agonist VC posture matching, the participant's fingers contacted the base of his hand, reducing ROM compared to antagonist VC. More work is needed to understand the effect of baseline phantom sensation on VC and PNS-evoked proprioception.

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Nanosymposium

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Topic: F.05. Brain-Machine Interface

Support: This project has been supported in part by the West Virginia University Center for Foundational Neuroscience Research and Education, as well as NSF grant 2242771 RII Track 1: West Virginia Network for Functional Neuroscience and Transcriptomics.

Title: A predictive CPG-like control to improve locomotor coordination during walking with a powered knee prosthesis

Authors: *S. TAHMID, S. YAKOVENKO;
Human Performance - Exercise Physiol., West Virginia Univ., Morgantown, WV

Abstract: Powered prosthetic knees can mitigate locomotor deficits in above-knee amputees, but controlling them is challenging because torque output must adapt to real-time dynamic demands. A feedback-driven finite-state approach that switches torque modes at discrete gait events can produce abrupt transitions and limit adaptation across walking speeds. Alternatively, a hybrid predictive-reactive system is theoretically optimal compared with a reactive-only system. We developed a continuous-phase controller with a predictive element, inspired by the central pattern generator (CPG), that replaced discrete states with a smooth gait-phase estimate to drive physiologically grounded knee torque profiles. Prosthetic-side vertical ground reaction force was used to detect heel strike and toe-off, while a velocity-driven phase oscillator estimated continuous gait phase between heel strikes using a dynamical phase-estimating model. The phase estimate indexed a mass-normalized torque profile scaled to body mass. The preliminary testing was completed using a knee bypass adapter at two slow speeds (0.5 and 0.8 m/s) while walking on a treadmill. The CPG-based decoder tracked gait phase with little drift and generated the intended biphasic torque profile. Preliminary results show that a simple CPG-based controller can provide continuous, speed-adaptive knee assistance without degrading gait kinetics or balance.

Disclosures: S. Tahmid: None. **S. Yakovenko:** None.

Nanosymposium

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Topic: F.05. Brain-Machine Interface

Support: This work was supported by the Air Force Office of Scientific Research (Award No. FA9550-24-1- 329 0208)

Title: Modulating neuromuscular control using localized vibration of multiple muscles to improve stability during standing and locomotion

Authors: *S. SHULTZ[1], S. YAKOVENKO[2];
[2]Human Performance, [1]West Virginia Univ., Morgantown, WV

Abstract: The sensorimotor loop of movement control implies that sensory pathways can shape and actively play a servo role. This implies that signals originating within sensory pathways can drive movement, offering an alternative to traditional methods such as functional electrical stimulation. Noninvasive technologies using electrical current have multiple limitations, including discomfort, skin irritation, rapid fatigue, and nonphysiological recruitment. Yet, the use of direct muscle and tendon vibration has been understudied due to technical limitations in specificity, habituation, and temporal delays. Previous studies have shown that humans sway anteroposteriorly when the tendons of the ankle joint's flexors or extensors are vibrated. The full-body sway has been attributed to primary muscle afferents, which cause proprioceptive illusions of muscle lengthening that influence postural control. The effects of vibration on musculotendon units during postural tasks, and on functionally related muscle groups during dynamic tasks, remain unknown. We hypothesized that coordinated, state-dependent vibration of functional muscle groups (flexors and extensors) increases whole-body stability by altering proprioceptive feedback to counteract applied perturbations. To test this hypothesis, we developed a simplified neuromechanical model incorporating muscle spindle feedback, informed by experimental testing of vibration-evoked perturbation responses during standing. Simulations showed that increased vibration amplitude led to higher stabilizing gains. The whole-body 'slip' perturbations with rapid anteroposterior platform (motorized treadmill) displacement were consistently stabilized, supporting the idea that vibrotactile stimulation of functional groups can improve postural control. Compared to baseline, the center of pressure (COP) analysis showed a notable reduction in average recovery time and peak displacement, which increased with greater vibration intensity, consistent with the model prediction of reduced feedback requirements. Moreover, preliminary analysis of 'catch' trials during walking with functional vibrotactile stimulation delivered to ankle, knee, and hip muscles shows that this type of feedback was incorporated with a servo role within the locomotor patterns. Based on these preliminary results, functional vibrotactile stimulation could improve postural stability, with prospective applications in rehabilitation and fall prevention for individuals with reduced proprioception due to injury or advanced age.

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Nanosymposium

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Presentation Number: NANO49.14

Topic: F.05. Brain-Machine Interface

Title: Modality-Invariant Cortical Decoding of Generative Semantics Across a Large Intracranial Cohort

Authors: *A. SINGH[1], E. MURPHY[2], N. TANDON[3];
[1]UT Hlth., Houston, TX; [2]Univ. of Texas Hlth. Sci. Ctr., Houston, TX; [3]Neurolog. Surgery, McGovern Med. Sch. at UT Hlth., Houston, TX

Abstract: The human brain encodes meaning through a hierarchy of symbolic representations: semantic features are selected via lexical forms that are articulated with motoric and phonological effectors. Each representation is dissociable through cortical motifs: signatures of high gamma across temporal, frontal, and parietal cortices uniquely encoding a set of linguistic features across periods of natural discourse in comprehension and production. Damage to this network results in devastating forms of aphasia, which current brain-computer interfaces are inadequate for given their constrained sensorimotor coverage. Motor cortex may be structurally unavailable, and even when intact, decoding articulatory output does nothing to restore semantics representations. No large-scale intracranial study has systematically characterized linguistic meaning from an information-theoretic perspective, defining how a genuine language BCI would operate.To address this, we recorded sEEG from 25 epilepsy patients reading or listening to sentence definitions that progressively constrained a target concept. We introduce surface-based linear mixed effects models (sbLME) that afford the unique ability to simultaneously resolve nested timecourses across orthogonal factors (e.g., word frequency, contextual integration), while regressing out subject-specific effects. Temporal generalization matrices identified which neural features spanned the comprehension to production axis in a modality-invariant manner for semantic, lexical, and phonemic decoding. Semantic features were projected across a broad space, covering locations, actions, emotions, tools, objects, and greetings. Non-negative matrix factorization of channel contributions over time yielded canonical cohort-level decoding motifs for these targets.sbLME encoding models and linguistic decoders converged on a standardized surface topology of semantics: inferior frontal and premotor cortices represented lexical features, while lateral temporal cortex encoded progressive reduction of semantic uncertainty regardless of cue modality, reflected in ramping decoder motifs. Semantic category decoding generalized across modalities (58.6% reading-to-listening, 42.1% for reverse; chance: 14.3%, $p<0.001$), temporally dissociable from lexical-phonemic decoding. These findings provide the first large-scale intracranial account of how the brain transitions between linguistic scales - not only across cortical space and time, but in the network-level motifs that operationalize a distributed neural interface designed to target meaning rather than movement in individuals with aphasia.

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Nanosymposium

NANO50: Neural Mechanisms of Human Emotional Processing

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO50.01

Topic: H.04. Emotion

Title: A grid-like code organizes affective space in human ventromedial prefrontal cortex

Authors: *Y. MA, P. A. KRAGEL;
Emory Univ., Atlanta, GA

Abstract: Human emotional experiences vary widely in everyday life, yet they are systematically organized within a continuous affective space defined by valence and arousal. Although this circumplex organization has shaped decades of research, its neural implementation remains unclear. Here, we asked whether abstract emotion concepts are encoded using grid-like coordinate principles in the human brain. During fMRI, participants tracked trajectories through affective space conveyed through morphs of facial expressions and sequences of phrases. We found that ventromedial prefrontal cortex (vmPFC) encoded affective space with robust hexadirectional modulation characteristic of grid-like coding. This coordinate representation generalized across stimulus modalities, indicating abstraction beyond perceptual features. The grid-like signal reflected a stable metric organization of emotion concepts independent of overt behavior, whereas distance-related signals in vmPFC predicted trial-by-trial affective judgements. Together, these findings suggest that emotion knowledge is structured by a grid-like coordinate system in the human brain that can support predictive inference and flexible decision-making.

Disclosures: Y. Ma: None. **P.A. Kragel:** None.

Nanosymposium

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Topic: H.04. Emotion

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Title: Visual Emotion Perception in a Deep Neural Network with Both Bottom-Up and Top-Down Connectivity

Authors: *P. LIU[1], K. BO[3], Y. CHEN[1], A. KEIL[4], M. DING[4], R. FANG[2];
[2]Biomed. Engin., [1]Univ. of Florida, Gainesville, FL; [3]Dept. of Psychological and Brain Sci., Dartmouth Col., Lebanon, NH; [4]Univ. Florida, Gainesville, FL

Abstract: The perception of opportunities and threats in complex visual scenes is a core function of the human visual system. The underlying neurophysiology has been extensively studied using affective pictures, revealing distributed brain responses to emotional content. The advent of deep neural networks (DNNs) offers new computational tools to probe these processes; however, most models treat emotion perception as a purely feedforward process, overlooking the dynamic interplay between internal states, external goals, and sensory input that are fundamental to

human emotion perception. To address this gap, we introduce EmoFB, a biologically inspired model that couples an affective system with a hierarchical visual pathway through both feedforward (bottom-up) and feedback (top-down) connections. We implement two forms of top-down modulation: intrinsic feedback, arising from the model's intrinsic appraisal of the visual input, and external steering, conveying contextual priors such as task requirements. EmoFB was evaluated on three emotion recognition tasks of increasing perceptual difficulty (Single Image, Side-by-Side Images, OverlayedImages). Results show that external steering enhances recognition performance under challenging conditions by sharpening the representational geometry of emotion categories in the model's feature space. Furthermore, external steering improves brain-model alignment, as evidenced by higher representational similarity between EmoFB and human fMRI responses in early visual cortex, ventral visual areas, and the amygdala. Together, these results demonstrate that top-down modulation enabled by feedback connections plays an important role in visual emotion perception, consistent with empirical neuroscience findings. EmoFB thus provides a computational framework that advances biological realism in the modeling of visual emotion perception and offers a platform for testing neurocognitive theories at the intersection of affective neuroscience and artificial intelligence.

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Nanosymposium

NANO50: Neural Mechanisms of Human Emotional Processing

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Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

Presentation Number: NANO50.03

Topic: H.04. Emotion

Title: Arousal effects on whole-brain functional network integration depend on emotional valence

Authors: *Y. TONG[1], J. PARK[1,2], Y. LEONG[1,2,3];
[1]Dept. of Psychology, [2]Inst. of Mind and Biol., [3]Neurosci. Inst., Univ. of Chicago, Chicago, IL

Abstract: Recent work has shown that heightened arousal promotes functional integration across large-scale brain networks, a brain state characterized by increased intermodular connectivity. However, it remains unknown how emotional valence, a second core affective dimension reflecting the degree to which an experience is positive or negative, influences these network dynamics. Here, we test whether the effect of arousal on whole-brain functional integration depends on emotional valence. We used an fMRI dataset where human participants (n = 27) viewed 14 audiovisual films spanning a variety of emotional content, and computed the functional connectivity matrix in each 30s segment for each participant. For each brain region, we computed the Gini coefficient of its connections across functional modules as a measure of how unevenly the region distributed its connections among modules. Using Bayesian multilevel models with behavioral ratings of valence and arousal for each segment, we found that

heightened arousal was associated with greater integration, reflected by lower Gini values, whereas valence showed no main effect. A model including the arousal by valence interaction revealed that the effect of arousal on integration was moderated by valence (posterior prob. > 0.99). Specifically, arousal was associated with greater network integration for more positively valenced segments but reduced network integration for more negatively valenced segments. To characterize how these effects varied across the cortical hierarchy, we ordered brain regions along an axis spanning from unimodal sensorimotor cortex to transmodal association cortex (Margulies et al., 2016). For positively valenced segments, arousal effects on integration followed a U-shaped pattern along the gradient, with stronger effects in both unimodal sensorimotor and transmodal association cortex. For negatively valenced segments, the pattern was linear, with reduced integration most pronounced in unimodal sensorimotor cortex. These findings suggest that high arousal positive state may facilitate broadened cross-network communication, whereas high arousal negative state may promote local processing, particularly within sensorimotor networks. Together, these results characterize how core affective dimensions jointly tune the balance between integration and segregation in the brain. Our study highlights the importance of considering both valence and arousal when characterizing how emotion influences large-scale brain organization.

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Nanosymposium

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Presentation Number: NANO50.04

Topic: H.04. Emotion

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AG19724

Title: Parasympathetic Co-modulation of the Human Heart and Face

Authors: F. NOOHI[1], N. BLOCK-WHEELER[1], L. PASQUINI[2], I. SIBLE[1], G. F. VOLK[4], J. KRAMER[3], B. MILLER[5], W. W. SEELEY[6], ***V. E. STURM**[1];
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Abstract: The parasympathetic nervous system plays a central role in emotions and social communication. The vagus nerve, the main conduit of the parasympathetic nervous system, influences the face as well as the heart, but its role in facial behavior is not well understood. Here, we examined whether parasympathetic activity related to the size and movement of *orbicularis* oculi, a muscle that encircles the eyes and contracts during positive emotions. We also investigated whether facial muscle size related to gray matter volume and functional connectivity in parasympathetic and motor brain networks. Twenty-three healthy adults completed a laboratory assessment that included measures of baseline physiology and positive emotional reactivity. They also underwent structural and functional connectivity neuroimaging. The volumes of ten emotion-relevant facial muscles were computed from manual tracings of the structural brain scans. Results indicated that individuals with smaller *orbicularis oculi* had greater variability in both resting heart rate, as measured by respiratory sinus arrhythmia, and smiling behavior in response to positive emotion-inducing stimuli. Individuals with smaller *orbicularis oculi* also had more synchronized activity in the heart and face and greater functional connectivity between brain networks related to parasympathetic and sensorimotor functions. The neuroimaging analyses further revealed that smaller *orbicularis oculi* was associated with gray matter volume within, and functional connectivity between, the parasympathetic and sensorimotor networks. Next, we examined whether *orbicularis oculi* size was altered in 21 individuals with the behavioral variant of frontotemporal dementia (bvFTD), a neurodegenerative disorder that targets the parasympathetic system. Consistent with prior studies, baseline RSA was impaired in people with bvFTD. The size of *orbicularis oculi*, however, was larger in the participants with bvFTD than in the healthy controls, and larger *orbicularis oculi* was associated with less variable movement during smiling. Structural neuroimaging analyses in participants with bvFTD revealed that larger *orbicularis oculi* size was associated with smaller gray matter volume in regions important for parasympathetic control yet larger gray matter volume in the sensorimotor network. These results offer a new window into the neurobiological basis of visceromotor linkage and suggest the parasympathetic system influences the structure and function of *orbicularis oculi*, a facial muscle integral for human emotions.

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Nanosymposium

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Topic: H.04. Emotion

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R01MH122431

Title: Functional organization of the human central autonomic network subserving emotional responses

Authors: *P. HULLETT, Q. R. GREICIUS, A. LIN, J. GEYFEN, M. BIJANZADEH, E. F. CHANG, V. E. STURM;
Univ. of California, San Francisco, San Francisco, CA

Abstract: The functional organization of the human cortical central autonomic network (CAN) remains incompletely understood despite many years of investigation. Clarifying this organization is important because dysautonomia is a prominent feature of many neuropsychiatric and neurologic disorders. A more precise understanding of CAN organization could provide insight into disease mechanisms and inform the development of spatially targeted therapies. However, several substantially different models of CAN organization remain in the literature, indicating a need for further clarification. To address this question, we used high-density bilateral intracranial recordings obtained during presurgical epilepsy evaluation. Six participants with extensive frontotemporal and insular coverage viewed a mean of 161 (±41 SD) emotion-eliciting video clips evoking amusement, disgust, awe, fear, sadness, or nurturant love while phasic electrodermal activity (EDA; sympathetic measure), and respiratory sinus arrhythmia (RSA; parasympathetic measure) were recorded. Using these data, we derived participant-specific network models that predicted second-by-second autonomic outflow from neural activity with high accuracy. Across participants, neural models predicted sympathetic and parasympathetic activity with mean correlation coefficients of 0.39 ± 0.12 and 0.33 ± 0.18, respectively. Group-level analysis revealed a consistent organizational principle within the cortical CAN. Midline regions, including the dorsal anterior cingulate cortex, were preferentially associated with sympathetic control, whereas more lateral cortical regions were preferentially associated with parasympathetic control. This data integrates and extends previous models of autonomic control by providing a new *medial-lateral* organizing principle for emotion-related autonomic regulation. To independently assess functional organization, direct electrical stimulation mapping was performed in 13 additional participants. Stimulation elicited autonomic responses that demonstrated the same medial-lateral pattern, providing causal evidence for a predominantly midline sympathetic and lateral parasympathetic organization of the human cortical CAN. Collectively, these convergent findings from predictive network modeling and causal stimulation mapping support a previously unrecognized medial-lateral functional organization of the human central autonomic network underlying emotional responses. This framework may advance investigation of dysautonomia across neuropsychiatric disorders and provide a foundation for future spatially targeted therapies.

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Nanosymposium

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JSPS KAKENHI Grant 23K17182

Title: Mapping the Representational Alignment Between AI Models and fMRI Activity

Authors: *J. CHIKAZOE, T. Q. PHAM;
Hiroshima Univ., Hiroshima, Japan

Abstract: Humans possess the remarkable cognitive ability to derive subjective valuations and aesthetic judgments from complex sensory events, such as viewing art or listening to music. Although artificial neural networks (ANNs) can now be trained to perform similar valuation tasks, the underlying mechanisms of these "sensory-to-value" transformations in both the human brain and AI models remain largely elusive. This presentation integrates findings from two distinct fMRI investigations—spanning visual and auditory domains—to elucidate these mechanisms by systematically comparing the internal representations of artificial models with human neural activity.In the visual domain, we examined convolutional neural networks (CNNs) optimized to predict human aesthetic valuations of paintings. Using multivoxel pattern analysis to evaluate the relationship between CNN representations and fMRI data, we identified a clear hierarchical mapping. Computations in the shallow CNN layers strongly correlated with activity in the primary visual cortex, while representations in deeper layers corresponded to higher association cortices and the default mode network (DMN).To investigate whether this functional architecture generalizes across sensory modalities, we integrated these results with a parallel fMRI study using neural networks trained to predict subjective ratings of music. Remarkably, the auditory domain demonstrated an analogous hierarchical transformation. Shallow layers of the music-predictive network matched stimulus-driven responses in the primary auditory cortex, reflecting basic acoustic feature extraction, whereas deeper, value-predicting layers aligned profoundly with the DMN and higher-order emotion networks.Together, these results provide compelling evidence that sensory-to-value transformations operate through a conserved, hierarchical process regardless of the sensory modality. This process closely mirrors the brain's principal gradient, transitioning from unimodal sensory regions to transmodal valuation networks. Consequently, the "black box" hidden layers of deep neural networks can be deciphered and visualized through their representational correspondence with fMRI activity. This cross-modal synthesis fundamentally strengthens the bridge between artificial intelligence and cognitive neuroscience, offering a unified framework for understanding the neural basis of human aesthetic experiences.

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Nanosymposium

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Title: The temporal organization of memory and emotion is reciprocally coupled

Authors: *M. LI, B. GIESBRECHT, R. C. LAPATE;
Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Emotional experiences unfold over time and can bias the appraisal and memory of subsequent events. Yet, it remains unclear whether and how the temporal organization of memory regulates the persistence of affect over time, or affective spillover—and conversely, how emotional-valence dynamics sculpt temporal memory. It also remains unknown whether nonstationary alpha bursts—recently implicated in automatic tracking of time during rest—likewise index online temporal memory coding during emotional experiences. To address these questions, we developed a novel paradigm employing positive and negative emotional sequences and combined EEG and behavioral measures of temporal memory and affective spillover. Participants (N = 51) viewed emotional sequences comprising four positive or negative images interleaved with novel neutral-face presentations. Following each sequence, they rated neutral-face likeability, indexing affective spillover. Transitions between emotional sequences were manipulated to induce emotional-valence shifts, and temporal distance and order memory were measured for images sampled from within and across sequences. Longer remembered temporal distance for image pairs sampled within sequences predicted reduced affective spillover onto neutral faces following those sequences, whereas better order memory predicted greater spillover. Alpha burst time during encoding correlated with longer remembered temporal distance and predicted reduced spillover following negative sequences. Conversely, valence transitions dilated remembered temporal distance and sharpened temporal order memory across event boundaries. These findings demonstrate reciprocal coupling between temporal memory organization and affect dynamics—highlighting the potential affect-regulatory role of temporal memory coding—and provide novel evidence that alpha burst dynamics sculpt the temporal organization of emotional experiences in memory.

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Nanosymposium

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Presentation Number: NANO50.08

Topic: H.04. Emotion

Support: NIMH Grant R37MH076136

Title: Probing the neural organization of affect with brain signatures: a large-scale multi-study evaluation

Authors: *M. KWON[1], P. A. KRAGEL[3], L. VAN OUDENHOVE[4], T. D. WAGER[2]; [2]Psychological and Brain Sci., [1]Dartmouth Col., Hanover, NH; [3]Psychology, Emory Univ., Atlanta, GA; [4]KU Leuven, Leuven, Belgium

Abstract: A central question in affective neuroscience is how affective processes are organized in the brain: by their affective content (e.g., "negative" vs. "positive affect"), or by other principles such as sensory modality and context. We used brain signatures, multivariate predictive models trained on fMRI data across individuals to predict specific affective constructs, as analytical probes to address this question.

We applied 29 signatures spanning pain, aversive, and appetitive processes to an independent multi-study fMRI dataset sampled from the database of the Affective Neuroimaging Consortium (ANiC; N=990; 66 studies) covering these domains plus cognitive control. For each signature, we computed pattern expression across domains to quantify cross-domain discriminability and reconstructed its encoding pattern using structure coefficients (Haufe et al., 2014). We then characterized the organization of these encoding patterns using hierarchical clustering and representational similarity analysis (RSA) regression, partitioning inter-signature similarity into affective-domain and sensory-modality contributions.

Pain signatures showed high cross-domain specificity and convergent encoding (within-domain r=0.41), whereas aversive and appetitive signatures showed cross-domain responses and low within-domain convergence (r=0.06 and 0.01). RSA regression showed that affective domain and sensory modality each predicted inter-signature similarity, explaining comparable and largely non-overlapping variance. The domain effect was predominantly driven by the pain domain rather than by valence, and the modality effect by the somatic and visual modalities. Data-driven clustering grouped the signatures into clusters aligned with distinct neural systems: visual, somatosensory/interoceptive, and reward-neuromodulatory networks, with reciprocal cross-modal suppression between the visual and somatosensory clusters.

These findings indicate that the neural organization captured by these fMRI-based predictive models is jointly shaped by affective content and sensory modality as independent axes, with modality as influential as content. This is consistent with accounts in which affect emerges from distributed, context-dependent processes rather than dedicated domain-specific circuits. Whether this organization reflects the structure of affect itself (e.g., affect embedded in modality-specific sensory systems) or the resolution of current population-level signatures (e.g., a bias toward signal consistent across individuals) remains open, and individual-level models could help distinguish the two.

Disclosures: M. Kwon: None. **P.A. Kragel:** None. **L. Van Oudenhove:** None. **T.D. Wager:** None.

Nanosymposium

NANO50: Neural Mechanisms of Human Emotional Processing

Location: WCC Rm 144

Time: Wednesday, November 18, 2026, 1:00 PM - 3:30 PM

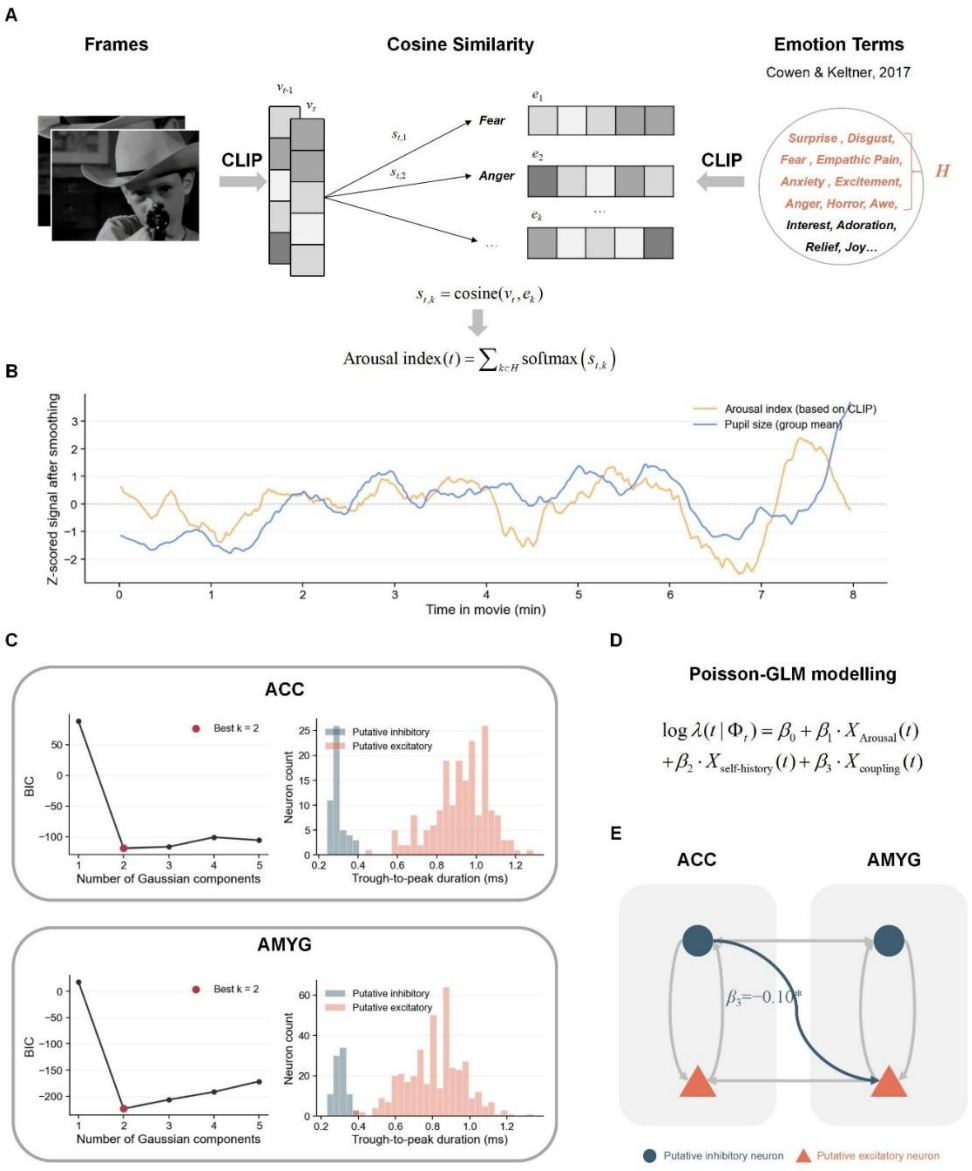
Presentation Number: NANO50.09

Topic: H.04. Emotion

Title: Directed ACC-amygdala interactions between putative E/I neurons during naturalistic viewing

Authors: *C. GAO[1], H. ZHOU[2], F. GENG[3], Y. HU[1,2];
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Abstract: Emotion and cognitive control are thought to be coordinated through signaling between the amygdala and anterior cingulate cortex (ACC). How excitatory (E) and inhibitory (I) neurons in these regions influence one another in humans remains unclear, as prior evidence lacks single-neuron, cell-type, and directional resolution. We analyzed single-neuron recordings of amygdala and ACC in 15 patients (9 female; 17-67 years) viewing an 8-min film from a public dataset (Keles et al., 2024). A Gaussian-mixture model of spike-waveform trough-to-peak duration classified neurons as broad-spiking putative E or narrow-spiking putative I, following prior criteria (Trainito et al., 2019). We used the group-mean pupil size indexed arousal: it was reliable across viewers (one-to-group r=0.65, p<0.001) and tracked a CLIP-derived film arousal index (r=0.51, p<0.001), peaking at a 1.2-s lag. Directed cell-type interactions were tested with point-process Granger causality (Kim et al., 2011). For each pair, nested GLMs assessed whether source spiking history improved target-spike prediction beyond target history and arousal (indexed by group-mean pupil size). Linear mixed-effects analysis of coupling coefficients showed a significant inhibitory influence from putative I ACC neurons to putative E amygdala neurons (mean β=-0.10, p=0.049), suggesting a single-neuron pathway through which control circuits may suppress affective processing in the human amygdala.



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Nanosymposium

NANO50: Neural Mechanisms of Human Emotional Processing

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Presentation Number: NANO50.10

Topic: H.03. Motivation

Support: NIH Grant 2T32AG000037

Title: Interpersonal reappraisal reveals limits of a simple load-sharing account of emotion regulation in couples

Authors: *B. MARTINS[1,2], A. GANAPATHI[2], I. PAREDES[2], J. CHU[2], P. J. KO[2], E. RODRIGUEZ[2], J. CROSTHWAIT[2], Z. NISHINO[1];
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Abstract: Emotions are often regulated with partners, but who does the work? Social Baseline Theory proposes that social resources reduce the effort required to manage threat, motivating a load-sharing hypothesis in which more demand falls on the person providing support. Interpersonal reappraisal occurs when one person offers another a less negative interpretation of an upsetting event. Receiving a loved one's reappraisal can reduce negative affect more than unaided reappraisal. Yet it remains unclear whether this benefit reflects simple offloading or a division of work across partners.We analyzed EEG recordings from 28 romantic couples completing an interpersonal emotion regulation task (56 adults aged 20-75 years, M = 39.71, SD = 19.86). Partners viewed negative images at T1. At T2, one partner generated either an objective description or reappraisal of the image while their partner waited. The statement was then shared at T3. Roles were randomized, with 36 trials per strategy. Load-sharing at T2 was indexed by sharer-minus-listener differences in 9-point effort ratings and frontal late positive potential (LPP) amplitude. Positive values indexed a more sharer-weighted pattern. For each couple and strategy, we estimated the perceived effort-difference slope across trials, then tested whether it predicted mean frontal LPP differences and listener self-reported arousal reductions from T2 to T3. For LPP, age-adjusted regression models with observations clustered within couples revealed a significant effort slope-by-strategy interaction (b = -28.27, SE = 10.22, p = .006). During description, shifts toward greater sharer effort predicted more sharer-weighted LPP (b = 13.43, SE = 5.24, p = .010). In contrast, during reappraisal, shifts toward greater sharer effort predicted more listener-weighted LPP (b = -14.84, SE = 7.22, p = .040), indicating greater listener neural engagement as subjective burden shifted toward sharers. For arousal, shifts toward greater sharer effort predicted reductions in listener arousal during description (b = .052, SE = .015, p < .001), but not reappraisal (p = .407).Our findings indicate that interpersonal regulation is not fully explained by a simple load-sharing model. While description was more consistent with direct offloading, reappraisal showed a split between subjective burden and neural preparation. Interpersonal emotion regulation may redistribute parts of the work across partners rather than move all demand from recipient to provider. Future work should examine how relative effort is distributed across relationships (e.g., friends, strangers) and other regulation strategies (e.g., distraction, validation).

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

Location: WCC Rm 143

Time: Wednesday, November 18, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO51.01

Topic: J.06. Computation, Modeling, and Simulation

Support: HHMI
Simons Foundation Collaboration on the Global Brain
NIH

Title: A connectivity-based cell type atlas of the larval zebrafish brain

Authors: *Q. WANG[1], S.-Y. TAKEMURA[1], M. PETKOVA[2], A. B.-Y. CHEN[2], N. IYER[1], W. T. KATZ[1], J. CLEMENTS[1], D. J. OLBRIS[1], S. BERG[1], S. ROMANI[1], R. SCHALEK[2], S. TURAGA[1], J.-M. LUECKMANN[3], M. JANUSZEWSKI[3], W. KORFF[1], V. JAIN[4], J. W. LICHTMAN[2], F. ENGERT[2], G. W. MEISSNER[1], C. KNECHT[1], M. B. AHRENS[1];
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Abstract: A whole-brain vertebrate connectome and functional recordings from the same larval zebrafish now let us ask how structure gives rise to function across an entire nervous system. This requires knowing the circuit role of every neuron, and a neuron's circuit role is defined by who it connects to. We therefore group neurons into cell types by their connectivity — the basis on which structure shapes function, and one that only a complete connectome makes accessible. We present the first purely connectivity-based cell-type map covering an entire vertebrate brain, preliminarily comprising 2,831 types across 140,349 neurons (median 30 neurons per type, up to 1,209). Types are discovered from connectivity alone. Neurons fall into the same type when they connect to the rest of the brain in the same way, so that moving any neuron into a different group would only make its connectivity fit worse — and the same grouping emerges regardless of how the algorithm is initialized. We achieve this by combining complementary community-detection methods — Bayesian-inferred stochastic block models, spectral embedding of connectivity profiles, and modularity maximization — into a consensus partition, which an LLM-assisted proposer-reviewer loop then refines against the connectivity evidence. To broaden access, we provide an interactive dashboard that brings these graph community-detection methods to the wider neuroscience community, letting researchers with no computational background re-cluster any brain subregion while incorporating their own external information. The pipeline has been integrated into the connectome's proofreading effort, yielding a ~4-fold speed increase. Using this atlas, we will examine how connectivity-defined cell identity explains brain function, leveraging the whole-brain functional recordings available for the same animal. Because cell identity spans many dimensions, we will also investigate where connectivity-defined types converge with or diverge from those defined by activity, development, anatomy, or molecular signaling — with each agreement and discrepancy illuminating how these dimensions relate.This collective effort will deliver the first connectivity-based cell-type atlas of a complete vertebrate brain.
Proofreading team: Nneoma Okeoma, Michael Cook, Alanna Lohff, Shirley Lauchie, Satoko Takemura, Brandon Canino, Caroline Mooney, Meghan Leonard, Charli Maldonado, Iris Ali, Birava Patel, Gary Hopkins, Emily Phillips, Christopher Ordish, Claire Smith, Samantha Finley-May, Ashley Scott, Tansy Yang, Jennifer Rivas Salinas, Alexander Thomson, Miriam A Flynn, Imran Hameed, Tyler Paterson, Louis Scuderi, John Walsh

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

Location: WCC Rm 143

Time: Wednesday, November 18, 2026, 1:00 PM - 2:45 PM

Presentation Number: NANO51.02

Topic: J.06. Computation, Modeling, and Simulation

Support: U19NS104653
SCGB542943SPI
Howard Hughes Medical Institute

Title: A whole-brain larval zebrafish connectome reveals a context-dependent hindbrain oscillator for flexible locomotor control

Authors: *L. TAO[1], X. LIU[1], S.-Y. TAKEMURA[1], A. B.-Y. CHEN[2], M. PETKOVA[2], N. IYER[1], R. SCHALEK[2], C. KNECHT[1], S. BERG[1], W. KORFF[1], G. W. MEISSNER[1], J.-M. LUECKMANN[3], M. JANUSZEWSKI[3], V. JAIN[4], J. W. LICHTMAN[2], F. ENGERT[2], S. ROMANI[1], M. B. AHRENS[1];
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Abstract: Flexible locomotion requires motor circuits to adapt their dynamics to sensory context, task demands, and internal physiological state. In larval zebrafish, the anterior rhombencephalic turning region (ARTR) has been implicated in spontaneous left-right turn alternation and is thought to contain recurrent excitatory and inhibitory circuitry capable of generating switching dynamics. However, whether ARTR functions as an isolated oscillator for a fixed motor pattern or as a premotor circuit flexibly coupled to broader sensorimotor and modulatory networks remains unknown. Here, we leverage a community-generated whole-brain larval zebrafish structure-function dataset, in which whole-brain neuronal activity was recorded across multiple behavioral tasks before reconstruction of the same animal's connectome, to identify circuit pathways interacting with ARTR. We find that ARTR receives diverse inputs, including sensory-related pathways and hypothalamic projections that may convey motivational or physiological state. ARTR is also connected with anterior hindbrain circuits involved in sensorimotor integration and self-motion-related computations. Across behavioral contexts, ARTR exhibits task-dependent correlation patterns with these anterior hindbrain systems, suggesting that its functional coupling is flexibly reconfigured rather than fixed. In addition, subsets of ARTR neurons project to reticulospinal neurons and the inferior olive, consistent with

a role in shaping locomotor dynamics through downstream motor and cerebellar pathways. Together, these results identify candidate circuit mechanisms through which recurrent hindbrain circuitry integrates sensory, modulatory, and motor-related signals to support context-dependent locomotor dynamics.

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

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Presentation Number: NANO51.03

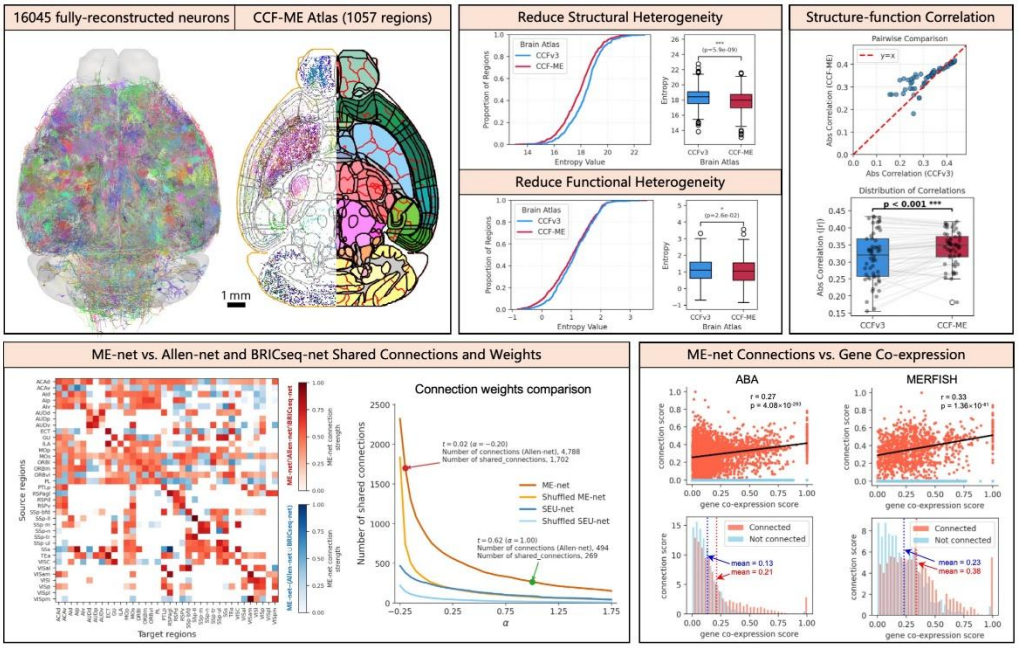
Topic: J.06. Computation, Modeling, and Simulation

Title: A cell-resolved CCF-ME mouse connectome links whole-brain wiring, physiology, and gene expression

Authors: *M. ZHAO, H. PENG;
Inst. for Brain and Intelligence, Fudan Univ., Shanghai, China

Abstract: Brain-wide connectomes have transformed systems neuroscience, but most current mouse connectomes remain constrained by mesoscale anatomical parcellations that average over heterogeneous neuronal populations. Here, we present ME-net, a cell-resolved mouse connectome built by integrating 16,045 fully reconstructed single-neuron morphologies into a refined whole-brain atlas, CCF-ME. Crucially, this approach increases effective anatomical granularity by more than 100-fold, driven by an expanded parcellation (1,057 regions in CCF-ME vs. 671 regions in CCFv3) and a massive scaling of fully-reconstructed single neuron data (16045 neurons vs. 1,877 neurons in SEU-net). To confirm that CCF-ME captures true biological diversity, we analyze 103,603 dendrite-reconstructed neurons from the NeuroXiv database and 75,708 high-quality single units from brain-wide Neuropixels recordings from the International Brain Laboratory. We demonstrate that CCF-ME significantly reduces both structural and functional within-region heterogeneity, and increases the structure-function correlations of single neurons within regions. Grounded in this validated atlas, our connectome, ME-net, not only preserves the macroscale wiring architectures of existed connectomes (e.g., Allen-net, SEU-net, and BRICseq-net) but also successfully uncovers high-resolution, cell-derived connections previously missed. Furthermore, to bridge structural wiring with its underlying molecular landscape, we map spatial transcriptomics onto our connectome. We find that ME-net exhibits strong organizational correlations with transcriptomic data, aligning with both the genome-wide Allen Brain Atlas (ABA) gene expression database (19,907 genes) and a single-cell gene expression dataset using multiplexed error-robust fluorescence in situ hybridization (MERFISH)

(1,122 genes). Together, these results establish a highly granular mouse brain connectome, providing a foundational dataset for linking multi-modal information across whole-brain wiring, physiology, and gene expression.



Disclosures: M. Zhao: None. **H. Peng:** None.

Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

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Presentation Number: NANO51.04

Topic: J.06. Computation, Modeling, and Simulation

Support: NIH U19NS104653
NIH 1R01NS124017

Title: Toward the vagal connectome: unraveling the integrated circuit mechanisms that control the body

Authors: *K. J. HERRERA[1], M. PETKOVA[1], A. B.-Y. CHEN[2], J. C. TAPIA[1], N. IYER[4], J. W. LICHTMAN[1], M. B. AHRENS[5], F. ENGERT[3], M. C. FISHMAN[6];
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Abstract: The vagus nerve (cranial nerve X) is a bidirectional neural pathway that enables the brain to sense and control a wide range of bodily functions, including cardiovascular, digestive, and immune processes. Through these interactions, the vagus nerve plays a critical role in maintaining an animal's homeostasis while dynamically shifting behavioral states to fit the ever-changing needs of the body. Yet, in contrast to other neural systems such as the retina, where detailed circuit maps have illuminated the computational motifs that define their function, little is known about how the anatomical principles that dictate how the sensory, motor, and intermediary interneurons are organized. Here we present progress toward a comprehensive vagal connectome in the larval zebrafish. Expanding from an initial volume of just the larval zebrafish brain that has been aligned to functional imaging data,we have appended an additional electron microscopy dataset that includes many of the vital organs that are innervated by the vagus nerve, including the gills, pharynx, pancreas, intestine, swim bladder, and heart. The targets of sensory neurons can be divided into two classes: 1) those that make localconnections and are upstream of vagal motor neurons, and 2) ascending neurons that innervate distributed regions of the brain and may potentially influence higher-cognitive processing. By integrating structure and function within the same animal, this work begins to uncover the organizational principles of the vagal systems and lays a foundation for building functional models that govern the body and how it interfaces with broader brain and behavioral states.

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

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Presentation Number: NANO51.05

Topic: J.06. Computation, Modeling, and Simulation

Support: U19NS104653
SCGB542943SPI
IOS-2508419

Title: Inferring neural interactions from dynamical solution spaces under connectomic constraints

Authors: *X. LIU[1], T. BISWAS[2], L. TAO[1], A. B.-Y. CHEN[3], M. PETKOVA[4], N. IYER[1], J.-M. LUECKMANN[6], M. JANUSZEWSKI[7], J. W. LICHTMAN[4], F. ENGERT[5], V. JAIN[8], M. B. AHRENS[1], J. E. FITZGERALD[2], S. ROMANI[1];
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Caesar, An Associate of the Max-Pl, Bonn, Germany; [7]Google Res., Pfaffikon SZ, Switzerland; [8]Brain & Cognitive Sci., Massachs Inst. Technol., Cambridge, MA

Abstract: How synaptic connectivity generates observed network dynamics remains a foundational question in neuroscience. To bridge this gap, we develop a framework for mapping the full solution space of recurrent networks with threshold nonlinearities that support prescribed time-varying neuronal dynamics, and for identifying regions of this solution space that are also consistent with empirical anatomical constraints.
We apply our framework to obtain a principled, mechanistically detailed understanding of the optomotor response (OMR) pathway in larval zebrafish, leveraging a dataset that combines simultaneous whole-brain, multi-task functional imaging with an EM connectome reconstructed from the same animal. Starting from pretectal sensory dynamics during OMR, we address a central circuit paradox: upstream retinal inputs carry only three motion-direction channels, whereas downstream pretectal populations represent four directions with complex temporal profiles. Specifically, forward motion drives dual-exponential kinetics, while other directions elicit a prolonged linear decay. By characterizing the continuous dynamical solution space under empirical connectome constraints, we prove that a purely linear network cannot achieve this dimensionality expansion under the observed input-output constraints. Instead, nonlinear recurrent interactions are mathematically required, demonstrating how nonlinear integration synthesizes the emergent direction representation while shaping its slow temporal decay.
We next demonstrate that the formalism can be applied across downstream circuit layers, such as from pretectum to nucleus of the Medial Longitudinal Fasciculus, a premotor population involved in forward swim generation, to test how pretectal representations are transformed into motor commands. Finally, by incorporating transcriptomic information and genetically or anatomically defined cell-type-specific gains that convert synapse counts to synapse strengths, we can assess whether network models exist that are consistent with both observed neuronal activity and connectivity. When transcriptomic information is not available, we may infer excitatory and inhibitory contributions at the morphologically and anatomically classified cell-type level. Together, our results in the optomotor sensorimotor pathway suggest that this framework provides a general strategy for inferring biologically plausible neural interactions from observed dynamics, recurrent circuit constraints, and connectomic structure.

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

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DoD W911NF2420112
Simons Foundation SCGB 542973
Simons Foundation NC-GB-CULM-00003241-02

Title: Connectome-constrained circuit mechanisms of locomotor control in zebrafish.

Authors: *Y. ISOE[1], A. B.-Y. CHEN[2], M. PETKOVA[1], M. JANUSZEWSKI[4], N. IYER[5], J. C. TAPIA[1], S. BERG[6], W. KORFF[7], J. W. LICHTMAN[1], V. JAIN[8], M. B. AHRENS[9], F. ENGERT[3];
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Abstract: Motor control is fundamental to animal behavior, requiring coordinated activation of muscles throughout the body. In vertebrates, rhythmic locomotion is generated by spinal central pattern generators (CPGs), while descending and spinal modulatory circuits adjust locomotor output to produce changes in speed, vigor, and turning bias in response to external demands. Although key neuronal components of these circuits have been identified through genetic, physiological, and behavioral studies in lamprey, zebrafish, and mouse, the network architecture underlying locomotor pattern generation and modulation remains incompletely understood. Here, we analyzed Fish 2.0, an electron microscopy-based connectome of a 6-day-post-fertilization larval zebrafish that includes the entire brain and the rostral spinal cord with four myotomes. Using soma position, soma size, organelle features, and axonal myelination, we identified 256 neurons of reticulospinal formation in the hindbrain and midbrain, approximately 700 motor neurons innervating rostral musculature, and ~1,700 spinal interneurons that were morphologically classified into distinct cell types. We then reconstructed connectivity across reticulospinal neurons, spinal interneurons, and motor neurons to reveal the core circuit architecture underlying locomotor control. Our analyses identify candidate network motifs underlying central pattern generation and suggest that locomotor pattern-generating circuits are embedded within broader modulatory networks that shape context-dependent motor output. In addition, we identified recurrent circuit structures that may support persistent neural activity and long-timescale motor-state regulation. Together, these findings provide a circuit-level framework for understanding how vertebrate nervous systems generate and flexibly control whole-body movement, and establish a foundation for realistic mechanistic models of locomotion and innate behavioral responses.

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Nanosymposium

NANO51: From Brain Connectivity Maps to Circuit Function: Computational Methods for Mapping, Inference, and Modeling

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Presentation Number: NANO51.07

Topic: J.06. Computation, Modeling, and Simulation

Support: JP23wm0625001
JP24wm0625406

Title: Large-Scale Spiking Neural Network Simulation of the Marmoset Cerebral Cortex Using Brain Atlas and dMRI Tractography

Authors: *J. IGARASHI[1], M. WANG[2], R. GONG[3], T. YAMAZAKI[5], S. ISHII[4];
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Abstract: Large-scale simulation of the marmoset brain offers a promising approach for understanding primate brain functions and disease mechanisms by integrating emerging multimodal datasets, including brain atlases, connectomes, and neuronal activity. A remaining challenge is to combine spatially resolved marmoset brain data with a spiking neural network simulator designed for high-performance computing. Here, we extended our in-house simulator, MONET, to construct and simulate a marmoset cortical network based on a brain atlas and dMRI tractography.
The model structure was defined using the marmoset brain atlas reported by Hata et al. (2020), and cortical layers were assigned voxel-wise based on cortical layer thickness and geometry. Given the conserved organization of mammalian cortical microcircuits and limited marmoset-specific local connectivity data, intra-regional connections were generated using rodent-derived cortical connectivity parameters (Igarashi et al., 2019).
Inter-regional connectivity was modeled using publicly available ex vivo marmoset dMRI data from the BRAIN/MINDS Data Portal. The dMRI data had an isotropic voxel size of 200 μm. Tractography streamline counts between voxel pairs were converted into connection probabilities and used to generate inter-regional connections.
Using the extended framework, we simulated eight cortical areas in the left hemisphere, including the dorsolateral prefrontal cortex, intraparietal sulcus region, primary motor cortex (M1), medial prefrontal cortex, posterior parietal area, premotor area, primary somatosensory cortex (S1), and ventral posterior parietal area. The model contained 16 million neurons and 600 billion synapses and was simulated on a workstation with 192 CPU cores and 3 TB of DRAM. When bias current was applied to layer 2/3 neurons in M1, neurons across cortical layers exhibited oscillatory activity at 30-50 Hz. S1 also showed traveling-wave-like activity induced by activation propagating from the stimulated M1 through inter-regional connections.
These results demonstrate that marmoset brain atlas data and tractography-based connectivity can be integrated into large-scale spiking simulations, providing a basis for studying inter-areal interactions and oscillatory dynamics in primate cortical circuits.

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